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THE PERSECUTED DRUG: THE STORY OF DMSO

BY PAT McGRADY, SR.

NEW REVISED EDITION

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THE PERSECUTED DRUG

THE STORY OF DMSO

REVISED AND UPDATED

PAT McGRADY, SR.

CHARTER
NEW YORK
A DIVISION OF CHARTER COMMUNICATIONS INC.
A GROSSET & DUNLAP COMPANY

TO GRACE—for her literary suggestions, and

TO MANY FRIENDS IN SCIENCE, MEDICINE AND GOVERNMENT—for their considerable help in gathering and interpreting a mountain of material,

This book is gratefully and affectionately dedicated.

THE PERSECUTED DRUG: THE STORY OF DMSO

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INTRODUCTION

In the forward of the hardcover edition (Doubleday, 1973), I described this book as representing "three stories in one: the incredible performance of an unbelievable drug; the unlikely adventures of a fantastic government agency; and the problems of a man so good in a wicked world that his virtues are regarded as vices."

The train of events since then has served only to confirm that position. The reports, as set forth, still stand; not one of them, so far as I have been able to learn, has been disproved. Moreover, scientists in several countries have reported new discoveries which embellish the excellent reputation of the drug, dimethyl sulfoxide, or DMSO.

There was one—and to my knowledge only one—serious challenge to the factuality of the claims I had cited in the hardcover book. That was a complaint voiced in an interview with *Medical Tribune* by James L. Goddard, M.D., the dynamic Commissioner of the U.S. Food and Drug Administration (FDA).

Admittedly activist by nature, Goddard gave the then-somnolent old FDA an air of purpose and dedication which it sadly had lacked. In a short time, the reborn bureau was advising drug houses which products they could and could

not peddle; it was telling physicians, in effect, how and how not to treat their patients; it was having growers and distributors recalling enormous amounts of provender which the FDA called dangerous. Goddard's G-men, initiating the "no-knock" technique, began raiding research laboratories and doctors' offices. Impressive was the fact that most of these sorties took place without warning or warrants. Something new was being introduced into our constitutional government.

Goddard took exception to my report of a long taped interview with him. *Medical Tribune* quoted Goddard as saying that "there are at least a few minor errors of fact in Mr. McGrady's book, along with more serious errors of interpretation and emphasis." The only specific and confirmable error that he cited was my statement that "in the 17 years since he had won his M.D., Goddard had been in private practice a total of 14 months. With this background, he was now to wield unprecedented, some charged almost dictatorial, power over the practice of medicine in the United States." Goddard's comment, according to *Medical Tribune*, was: "I was in private practice for 16 months, not 14, although I admit that's not very important."

To me, any charge that I have been inaccurate is important. I make occasional mistakes, and I am embarrassed by every one of them. But when I reviewed the tape, Goddard's voice come over loud and clear on his experience prior to joining Government service: "I submit to being in practice for 14 months and grossing over $20,000 a year." If this was my only "error"—and Goddard charged me with no other specific inaccuracy in his skimpy bill of particulars—then I could only conclude that my reportage was remarkably accurate and my interpretations fundamentally sound. While I feel certain I must have committed a few booboos in the book, a diligent search and questioning of scientists and physicians and others who played important roles in the story have failed to indicate a single significant error. I am con-

vinced that my report on "the incredible performance of an unbelievable drug" is accurate.

Goddard retired eventually, as so many of his predecessors and successors have done, to serve as an official in the drug industry which the FDA regulates. And he came to complain to and about the FDA for some of the practices he himself had initiated as Commissioner.

DMSO remains a truly amazing substance. It is a versatile solvent; it probably will dissolve more chemicals than any other solvent. It penetrates the skin and is in the bloodstream within seconds; and it carries many dissolved chemicals with it. It freezes at a couple of degrees below room temperature. As a runoff product of the paper industry, it is abundant and should be cheap. (With inflation and the middleman's profits, its price during the last half-dozen years has multiplied thirty fold. But considering its many uses, it still is cheap at the current $10 a pint.)

But the most amazing thing about DMSO is its effect on life. It prevents, controls or cures some of the diseases of man, animals and plants; no other drug or group of drugs has DMSO's multiplicity of uses. DMSO frequently is called the closest thing to a panacea that the world has ever seen. A great many of its medical applications were described in the hardcover edition of this book and will be repeated and updated in this edition.

Part One

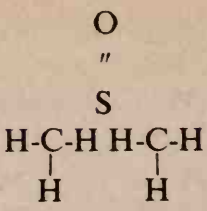
The year was 1866. The place was Kazan, even then an important city on the Volga River in Central Russia.

Dr. Alexander M. Saytzeff held a test tube up to the light and examined its contents. The stuff looked like water; it was colorless and clear; it had a barely perceptible scent of sulfur about it. He may have put a drop or two on a glass rod and tasted it; it was slightly bitter and left an oysterish or garlicky aftertaste and odor. His fingers felt it; it was a little viscous—not much. But decidedly there was something odd about it; it left the skin warm—almost hot; it had a drying effect on the tissues. He identified it as DMSO, or dimethyl sulfoxide.

Strangest of all was its avidity for other substances. It dissolved almost everything he added to it. Saytzeff put the fluid on his shelf, took it down occasionally to test its unusual physical and chemical qualities, and wrote a little article on its synthesis which appeared in 1867 in a journal published in Germany.

Saytzeff eventually went to his grave and his discovery, to all intents and purposes, was buried with him. For eighty or ninety years, it served as little more than as a conversation piece among chemists.

DMSO is a small and simple molecule, especially when one considers the impressive spectrum of its effects upon living and non-living matter—a versatility possibly unequaled by any other chemical designed by God or man.



It is composed of two methyl (CH_3) groups and a sulfur and an oxygen atom, all of them stacked up in the shape of a pyramid. The sulfur pole has a strong negative charge, and the oxygen a positive charge, and the resulting electromagnetic-type force enables one DMSO molecule to attach to another—negative pole to positive pole—and form molecular chains.

For eighty years, scientists did not go far beyond Saytzeff's rudimentary findings. Then, gradually, in scattered laboratories around the world, researchers started mounting investigations of its curious capabilities. The fact that DMSO began to have commercial value in a few industries made the research rewarding enough.

Some of the inquiry delved into the structure of DMSO itself—a molecular Gibraltar able to resist formidable forces which would swallow it, shatter it or in some way change it. It had sturdiness to spare; it stabilized neighboring compounds and even entire structures in living cells.

DMSO was found to be unique in its promiscuous embrace of other molecules, in the strength of its bonds, its imperviousness to cold, its striking propensity for giving off heat and for undoing the effect of radiations, its ghostlike ability to penetrate tissue and cell walls and to transport other substances with it. In probably unparalleled chemical compatibility, DMSO was shown to mix readily with other solvents—water, alcohol, oils (lipids) and benzene among them.

Some research was of a fundamental nature—as they say, to develop knowledge solely for the sake of knowledge.

Other studies were practical—to produce a better synthetic fiber or an improved solvent for resins, dyes, paints, or agricultural chemicals. DMSO production by United States pulp and paper mills began to mount sharply in the mid-1950's because of the solvent's increasing utility in various industries; by the mid-1960's, it had gone from a few thousand pounds a year to five million. The big stimulus stemmed from optimistic reports of DMSO's role in medicine.

The highly technical chemical data suggested to imaginative scientists a diverse therapeutic potential for DMSO.

DMSO freezes at about room temperature (a little more than 18° C or 68° F) and boils at a similarly high temperature (189° C or 372° F). Because it combines with water, it reduces ice-crystal formation. With this clue, British scientists discovered that DMSO was a gentle and effective coolant which permitted the storage of blood cells and their source, bone marrow. Even at 50° C below zero a 50 per cent mixture of DMSO and water will not freeze.

DMSO's abilities, at various concentrations, to donate protons to other molecules and to trap charged flying atoms and clusters of atoms (free radicals, so-called) permit it to maintain order amid the chaos of the dynamic micro-world of inner space. This suggested that DMSO might undo or prevent radiation damage to living systems.

DMSO has a great capacity to dehumidify locally by sopping water out of the environment. It gets rid of the water shell around many substances and then dissolves them—that is, it floods into the spaces between the solute molecules, delicately separating and suspending them. It does this for simple gases, resins (in some lacquers), sugars, cellulose derivatives and dextran, the blood plasma expander.

It also alters some antibiotics and the basic components of living matter—proteins and nucleic acids. This finding made DMSO a candidate for testing as a potentiator of preparations for disease control in humans, animals and plants.

In high concentrations, DMSO denatures, or demolishes,

the basic chemical components of life, nucleic acids and some proteins; it breaks them up so they can never be put together again. In low concentrations, DMSO may gently dissolve the same proteins and activate them. This dual influence on the proteins would endow DMSO with a vast potential of enzymatic effects. Enzymes are proteins which catalyze the many thousands of reactions in the body's essential chemistry. By activating or inhibiting various enzyme systems, DMSO presumably turns on and off various physical and mental functions. It is possible, for example, that by suppressing the enzyme cholinesterase, which catalyzes certain reactions in the C fibers of the nerves, DMSO might block the chemical pathway transmitting the pain sensation. Or DMSO might dissolve or denature a virus's protein coat of armor and leave the viral nucleic acid core, should it survive the DMSO onslaught, naked, defenseless and subject to attack by the host's immune arsenal. Some believe that this and any of several other properties might also sterilize or kill bacteria and fungi.

The simple solvent gradually has acquired a long and varied repertoire of other reactive talents on which an imaginative scientist could hypothesize numerous medical applications. DMSO's ability to chelate, or claw, certain metals out of molecules recommends it, theoretically, for a gamut of uses, from treating lead poisoning to correcting certain inherited disorders; it now is known to dissolve and partially detoxify some poorly absorbed quaternary ammonium solts. Its stabilizing effect on some of the cell's sources of ready-made enzymes (mitochrondria and lysosomes), its harmless handling of enzymes, its power to dissolve a great may essential body chemicals—fatty acids, sterols, polysaccharides, and the like—suggest that the uses of DMSO may be limitless. On research group has used DMSO to extract edible keratin proteins from goose feathers.

Investigators in widely scattered parts of the world have reported on the curious physical and chemical attributes of

DMSO: Austrians on the molecule's Raman spectra and polarization data, Scandinavians on its structure, Americans on its vapor pressure and thermodynamic properties, Canadians on its association with water, Finns on its behavior when mixed with benzene, Germans on its solvent abilities, Japanese on its use in synthetic manufacturing, and the British on DMSO's protection against damage by cold.

It was this last bit of information that climaxed a young American surgeon's search and projected him from the quiet of his ivory tower into a life of high adventure.

It was a large room on the sixth floor of the University of Oregon Medical School complex. It was brightly lighted, utilitarian, smelling of non-fragrant chemicals, and noisy with the clink of glassware, the splash of water in the large sink, the clatter of a typewriter, and the supersonic sensations emanating from laboratory machines.

A few young men and women worked at the long glass-strewn table. A secretary typed industriously at an orderly desk.

Two men were deep in conversation at a desk cluttered with journals, notepaper, records of various dimensions and a small stack of manuscripts.

The smaller man in the white coat, the surgeon, watched in fascination as the man in the brown suit, the chemist, rubbed India ink on a twig and then applied a colorless fluid to it. The fluid seemed to drive the ink into the twig.

"It does that with antibiotics too," the chemist said.

"How about human tissues?" the surgeon asked.

The chemist said, "It seems to penetrate to the deeper layers of the skin. A dermatologist at Stanford once told me that if it did that, they might have to rewrite the dermatology textbooks."

The episode, late in 1961, was to change the surgeon's life drastically. And the chemist's life. And the destinies of many others as well.

The chemist was Robert J. Herschler, who bore the title Supervisor, Applications Research, Chemical Products Division, Crown Zellerbach Corp., Camas, Washington. CZ is one of the biggest pulp and paper maufacturers in the world.. Camas is across the bridge from Portland and a half-hour's drive up the Columbia River.

The surgeon was Stanley Wallace Jacob, M.D., F.A.C.S., Assistant Professor of Surgery, University of Oregon Medical School.

Both men were thirty-seven years old. Herschler, a six-footer weighing 189–190 pounds, was five inches taller and thirty pounds heavier than Jacob. In their professions, their aptitudes, their life modes, their social and academic backgrounds, they were far apart. But in one thing—their complete zeal for and dedication to the watery stuff they were examining—they became identical twins.

Herschler was the hard-working son of hard-working parents. He paid much of his own way through high school in the state of Washington and through Washington University in St. Louis, Missouri, where he received his highest academic award—a Bachelor of Science degree. Soon after graduation, he got a job with Crown, and for twenty-odd years he had been a faithful—albeit often unhappy—employee of that concern.

With only a Bachelor of Science degree but endowed with considerable aptitude for chemistry and a nagging curiosity about biological phenomena, Herschler resided in an academic, cultural, and economic twilight zone reserved for over-qualified non-doctors. One of a familiar breed of talented untouchables in a degree-conscious community, Herschler was outranked in his firm by men he felt were less competent. He was a creature of an industrial colossus, he said, bound by unuttered vows of humility, obedience and silence. He was paid the wage which good—but non-doctoral—chemists command in a small town setting, and, with this and his wife's salary as a teacher, he had built a

good home with his own hands and maintained his family of three daughters in comfort. He reacted as any man does to orders which he considered less than reasonable; but he did what was required and held his job.

What hurt most, Herschler complained, was the silence imposed on him. It was not that the professional caste system carries a good deal of weight with doctor-conscious journal editors, it was the rigid censorship imposed by industry. Scientific data and ideas are treated in industry generally as trade secrets; and they are mentioned abroad only with the firm's consent—and usually to advance commercial ends. The chemist was exploding with ideas that needed uttering.

For more than a year Herschler had been seeking one of the academic elite—an M.D. or a Ph.D.—to discuss the interesting compounds he had teased out of trees as they were converted into newsprint and toilet tissue. One of the chemicals was DMSO. There were others which he felt might be of value in science and medicine.

For many months, Dr. Stanley W. Jacob had been seeking a way to cool his isolated dog hearts. He had stored the living organs under enormous pressures; he had tried a succession of antifreeze chemicals. Nothing stopped ice crystals from forming and killing the delicate cells.

When the British reported success with DMSO as a preservative for blood and marrow cells, he devoured every word he could find on the chemical and physical properties of DMSO. And now across the table sat a man who knew—and had—DMSO, a whole gallon container of it.

Unlike Herschler, Jacob had been blessed in abundance with professional privileges, triumphs and the trophies. He was a Fellow of the American College of Surgeons, an Assistant (soon to be Associate) Professor of Surgery in a department headed up by the prestigious Dr. J. Englebert Dunphy. He had held the emblem of all-around intellectual excellence, a five-year Markle Scholarship in Medical Sciences, an honor bestowed on those with towering IQ's.

Customarily he had been at the top of his class, or very close to it, in grade school in Atlantic City, N.J., and high school in Youngstown, Ohio. During his undergraduate years at Ohio State University, as a science major, he ranked first in his premedical class; he had his B.A. at age twenty-one and his M.D. (cum laude) at twenty-four—in 1948, the year Herschler got a job with Crown. He completed his internship, residency, and a three-year research fellowship at Harvard Medical School and its teaching hospitals and became the chief resident in surgery under Dunphy at Harvard's big and busy Boston City Hospital.

Herschler, his friends said, was a quiet, sober, sensitive, introspective sort. The fires of enthusiasm were great but they burned inside him—where they could not be quenched by what he felt were socially superior but intellectually superficial materialsts about him.

Jacob, on the other hand, was outgoing. In high school he was a cheerleader, and a Ping-Pong champion, senior class president, state champion in oratory and in debate. He was a member of a dozen scholarly and professional organizations, including Phi Beta Kappa, and Alpha Omega Alpha (the upper ten percentile, nationally). He was won such honors as the Kemper Foundation Research Scholarship of the American College of Surgeons (1957–60) and First Place Glycerine Research Award, 1959. He was a lieutenant colonel in the U.S. Army Medical Corps Reserve and had served in Japan during the Korean War. He had published more than forty papers in scientific journals on such research as overcoming surgical shock, the prophylactic use of antibiotics, and the problem of restoring blood production in leukemic children treated with lethal doses of radiation. (He was successful in restarting blood cell synthesis in lethally irradiated dogs by inserting a marrow-producing healthy rib into their spleens.)

At the time of his meeting with Herschler, Jacob was seeking a means of cooling viable organs from freshly dead donors; his idea was to preserve the hearts so that, when

needed, they could be taken out of cold storage and grafted into the recipient at once; this would replace the ghoulish practice of pacing the floor impatiently, waiting for the donor to die—or, worse, speeding his demise. Even at this early date, 1961, when heart transplants were discussed mainly in science fiction, Jacob and his team were making puppy hearts beat in adult dogs for several days at a time.

On this early winter afternoon, Herschler told Jacob of the day when DMSO solutions of basic dyes had been spilled accidentally; the color seemed to seep into deeper areas of the skin of workmen who had been splashed. When a DMSO solution of pesticidal DDT was spilled, those who were in the way became sick. Herschler told how DMSO solutions of antibiotics and antifungal agents had penetrated the surface of plants, and he surmised that DMSO might have a valuable place in treating plant diseases.

Late that evening, before he closed his lab, Jacob applied iodine to his arm, dabbed DMSO over the spot, and sat there watching the iodine disappear into the skin. As he watched, he suddenly became aware of a strange thing: He could taste the DMSO! This meant that DMSO not only went deep into the skin but actually went through the skin, into the bloodstream and throughout the system!

The young surgeon rose to his feet and paced the floor, a thousand ideas clamoring for recognition. Did DMSO open a new door from the outer environment into the body? Would DMSO serve as a train to transport drugs through the skin to the internal organs? Could it be that DMSO represented not merely a new drug but an entire new principle in the treatment of disease?

Jacob did not sleep well that cold night. He hasn't slept very well ever since. Visions held siege in the brain regions meant for dreams.

The next day Jacob applied DMSO to the backs of the hands of his lab staff. Most of them reported the garlicky

taste; the odor came quickly onto the breath of every one of them.

And some said the DMSO seemed to have a drying effect on the skin where it had been dabbed on. It occurred to Jacob that if this were so, DMSO applied to skin burns might prevent infections in the moist areas under scabs, a common and sometimes serious complication. He and Herschler set up a little experiment in which eighteen rats, under anesthesia, received scald burns on the back. The six treated with DMSO were much quieter and presumably more comfortable than the six treated with salt solution and the other six given no treatment.

The experiment had little if any scientific significance; but a little later, when Herschler sustained a chemical burn on his hands, forearms and forehead, DMSO was applied; the pain subsided in five minutes and stayed away for four hours, when a second application of DMSO again dispelled it.

When one of Herschler's assistants sprained an ankle, DMSO was applied liberally; the pain was relieved in fifteen minutes and the swelling in a half-hour.

An arthritic thumb was painted with DMSO, and in less than an hour pain and swelling were reduced.

Clinical experiments of this sort—each could be described as a "series of one case"—don't constitute scientific proof of anything. They did convince Jacob, however, that DMSO demanded urgent attention. He moved impulsively to seek new biological activities of the watery stuff. He worked tirelessly to confirm his observations in animals, then in humans—first of all, on himself.

Jacob rapidly came to recognize in DMSO not only its ability to pass into the skin carrying other substances with it, but he found further that DMSO would deposit many of these materials in the bloodstream, that it would pass through otherwise impenetrable membranes, that alone it possessed dramatic healing properties, and in combination with certain

other drugs, it exercised an additive or multiplying effect.

For him, his long workday now became much too brief. Dawn came too late; night—when wearily he would turn out the light in his lab and leave a deserted building and cross a silent campus—fell too soon.

As DMSO bared its chemical and biological secrets to him, one by one, Jacob became convinced that the strange tree juice offered the art and science of medicine a boon of major magnitude.

Convincing others was to be another matter.

It was not entirely by accident that Jacob happened to have DMSO with him on those numerous occasions when someone needed it. After testing the drug on himself with enormous doses and on willing associates with smaller—but still large—doses, the young surgeon carried a bottle of the drug in his coat pocket wherever he went.

On Army Reserve training, an enlisted man—a football player for Portland State College—told Jacob that he had a splitting headache and asked to be excused from a half-mile run. Jacob showed him some DMSO, told him a little about its properties, and asked if the enlisted man would mind if he dabbed a little on his forehead. The headache cleared up within minutes, and the man ran the half-mile. The headache returned after four hours and once again was suppressed with DMSO.

The chief nurse at a county hospital had Jacob apply DMSO to a painful cold sore on her upper lip. When she called him on the telephone a couple of hours later, Jacob said expectantly, "Dorothy, you're going to tell me that the DMSO dried up your cold sore and it's going away?"

"No," Dorothy said. "It's better than that. It cleared up a sinusitis I've been fighting without any luck. For the first time in three months I'm breathing normally and easily through that nasal passage."

For Jacob, life was becoming full of serendipity—surprise

discoveries, unexpected revelations, unsought disclosures.

There was the day an intern called Jacob's attention to Daisy, a skinny little six-year-old who for three years had lived in pain. She had rheumatoid arthritis in her neck and hip. On this occasion Jacob petted her out of her low-moaning misery and asked, "Honey, do you mind if I rub a little of this stuff where it hurts?" Because everything long ago had lost the power to assuage the pain, Daisy wasn't too keen about the idea, but finally she gave in. A half-hour later, the little girl turned her head and moved her shoulder. She hadn't been able to do that in two years.

After a good deal of coaxing, Daisy finally let herself be lifted from her crib; and, clinging to the surgeon's elbow with matchstick arms, she tottered on her wasted legs. Then, unsupported, she walked a few steps alone.

Daisy bawled. When the doctor asked whe she was crying, Daisy said happily, "Because it doesn't hurt any more."

There were failures, of course. Failures galore. The dose that seemed to work for one patient had no effect at all in another with an apparently identical condition.

And, Jacob knew, any of the individuals he had treated successfully quite conceivably could have been helped by a placebo effect. A placebo (from the Latin meaning "I shall please") is a sugar pill, or an injection of distilled water, or a teaspoonful of an innocuous (but preferably bitter-tasting) fluid. Somewhere between 20 and 50 per cent of cancer patients given a placebo will report feeling better, and a few of them may gain weight, eat better, sleep well or show other objective signs of improvement—for a while.

There was no way of telling for sure whether DMSO had exerted a true physiological effect or served as a psychological crutch in almost any of the patients Jacob treated. One would be naïve not to suspect that a placebo effect was involved in any one case of the instant clearing of headaches, the immediate improvement in arthritics, or any of the numerous other "miracles" that followed dabbing DMSO

n the skin. At the same time, one would have to be a mpleton to attribute all the remarkable effects solely to acebo properties.

Because, by and large, animals are less suggestible and erefore superior to humans as experimental subjects, Jacob nd his associates ran countless laboratory experiments. It as expedient, for example, to learn in the lab whether MSO would prevent adhesions from forming following rtain surgical procedures. At least there would be minimal notional effects involved in efforts to keep organs in the rat lly from sticking together or to the wound following a am operation. Dilute (15 per cent) DMSO was instilled to the body cavities of one half the operated rats for ten days ter surgery; nothing was done for the other rats. At the end the experiment, the animals were opened up and amined. Results: completely negative. There were just as any adhesions in the DMSO-treated rodents as in the con-ols.

Jacob mulled it over for a few days and wondered what le the timing had played. He repeated the experiment with ne change: he administered the DMSO before surgery, ther than after it. Result: DMSO greatly reduced the umber of adhesions.

It appeared that DMSO could suppress inflammation—a enefactive potential for both patient and doctor in countless fe-threatening and other worrisome situations.

DMSO was cheap—it could be produced for thirty-five nts a pint, and a pint represented, on the average, a month's enerous supply for most large households. Moreover, it uld be produced in any quantity, pretty much as a runoff oduct of the pulp and paper industry. "I could pipe it down re for you," Herschler once told Jacob. "You could have by the barrel or the tank."

Research, even on animals, is costly, however, and it soon came necessary for Jacob to scratch for financial support

well beyond the funds he could spare from his own salary. Some dealers in laboratory supplies were beginning to show impatience over past-due bills.

Jacob finally decided to appeal to his dean, Dr. David W. E. Baird.

Baird, who later retired, was regarded as an intelligent and charismatic head of the University of Oregon Medical School faculty. He encouraged creative ideas among those capable of developing them; he abided by principles of decent and tolerant human conduct for himself and sternly forbade any and all under his dominion from abridging the rights of others; he was bluff, amiable, sensitive to the needs and weakness of others, but, withal, a no-nonsense man.

Dean Baird listened attentively to the young surgeon, who had dressed for the occasion in a correct Ivy League-type suit, with manners to match. Jacob told the head of the school hierarchy how he became interested in DMSO, what he had done with it so far, and the role he hoped it would play in medicine.

"The trouble is," Jacob said, "I've diverted into this work all I can spare."

He paused for a long minute, as the older man leaned back in his swivel chair and studied him carefully. The dean had heard about DMSO; some of the reports and rumors had been carried to him as complaints from faculty members who neither relished Jacob's unrestrained enthusiasm for the drug nor approved his swashbuckling trials on a large number of unrelated pathological conditions. Some faculty members would be most unhappy if Jacob were encouraged. Nevertheless, when at length Dean Baird spoke, he said, "I think that the university might be able to spare a little support for something as promising as DMSO. Would five thousand dollars help?"

It would. And it did. Jacob had found a powerful benefactor.

The fortunes of DMSO were governed by the vagaries of chance in areas completely unrelated to the compound's role of science and medicine.

These factors were first interjected into the DMSO story—without anyone's being aware of the fact—on the morning of March 13, 1962, at a seminar for science writers in the Ramada Inn in odoriferous proximity to the slaughterhouse in San Diego, California.

George E. Moore, M.D., Ph.D., F.A.C.S., who had rebuilt the nondescript Roswell Park Memorial Institute of Buffalo, N.Y., into one of the world's most productive research centers, began his lecture by walking to the blackboard and writing in large block letters:

T-H-A-L-I-D-O-M-I-D-E

"Note that name well," he told the writers. "You'll be reporting it for some time to come."

Thalidomide was a drug produced in Germany—the perfect sedative, some have called it. It was said to have no aftereffects.

"What we have not been told is that thalidomide damages the unborn," Moore said. "Dr. Helen B. Taussig of Baltimore returned recently from Europe with information that between three and four thousand malformed babies have been born to German mothers who had been taking thalidomide during their pregnancies; between one and two

thousand additional cases have occurred in the United Kingdom."

Moore talked about cancer research at Roswell Park and then, already overdue for conferences at home, he headed for the airport and nosed his own plane toward winter and Buffalo.

Without opportunity to question Moore fully, only two of the writers mentioned thalidomide, and these references were brief and buried deep in their stories.

Four months later the story broke out of Washington—the FDA announcement commanded screaming eight-column bannerlines and page one play. Dr. Taussig said at the time, "We should be grateful the drug was not dreamed up in this country. It could have passed the Food and Drug Administration under our present laws."

President Kennedy a month or so after the news break pinned a medal on Dr. Frances O. Kelsey of the FDA for her heroic passivity in not favoring thalidomide in the long backlog of new drugs awaiting FDA approval. Inasmuch as thalidomide was not introduced abroad until 1958 and it was taken off the market late in 1961, Kelsey may not have had to exercise much restraint to save American embryos from phocomelia, the congenital deformity. The situation was not without a happy side: the story and picture of President Kennedy decorating Kelsey made page one and warmed the hearts of all good Americans, especially those in the FDA's corps of press agents.

Among those who heard Moore's brief account of thalidomide effects was Dr. Stanley W. Jacob of the University of Oregon, another speaker. He had not the slightest inkling at this time that thalidomide would play a crucial role in shaping his career.

Jacob the next day delivered a lively and scholarly dissertation—twenty-four pages of observations on his and his associates' attempts to preserve human spermatozoa, dog and rabbit skin, conjunctival cells and tissues by cooling

them to temperatures as low as minus 272.2° C and a score of other studies.

Jacob did not mention DMSO on this occasion. He had only begun serious studies with it.

Joan F. Giambalvo, M.D., of the FDA once drew up a chronology of the misery on which her agency had thrived prior to the thalidomide incident.

It took the deaths of ten children from diphtheria antitoxin contaminated with tetanus to impel Congress to pass the Virus, Serum and Toxin Act of 1902, the nation's first effort to regulate drug manufacturing. The existing law (of 1848) merely had prohibited the importation of adulterated drugs—a statute offering obvious advantages for American pharmaceutical houses.

The 1906 Pure Food and Drug Act was a consequence of Upton Sinclair's *The Jungle*, a stomach-turning account of meat-packing practices. At the same time, Dr. Harvey W. Wiley's "poison squad" of young U.S. Department of Agriculture employees exposed the incorporation of dangerous additives in food.

Additional restrictions were imposed after finding cataracts in more than 100 people who took dinitrophenol to reduce the mysterious female illnesses which finally were traced to thallium in a depilatory, and then, in 1937, the death of more than 100 people from Elixir of Sulfanilamide containing a highly toxic solvent, diethylene glycol. Congress reacted in 1938 by requiring that new drugs pass safety tests and that the data be submitted to the government for clearance. The 1938 law, while tending to assure the safety of drugs, did nothing to require their efficacy. Worthless preparations could be peddled freely so long as they were harmless.

Then came thalidomide.

In August of 1962, the proposed new FDA regulations were published for comment. They had been discussed for

years, but the teratogenic horror that swept over Germany and the United Kingdom made American action mandatory and urgent. Congress pressed the panic button.

The Kefauver-Harris Amendments called for extensive and expensive protocols in the basic testing of drugs—so expensive, in fact, that millions of dollars had to be poured into any drug's being tested, and so time-consuming they were unworkable in a bureau already years behind schedule. The FDA was given police powers like those exercised by gang-busting agencies; they called for intricate divisions and subdivisions of an organization already so intricately divided and subdivided and duplicative that it was unmanageable; they spawned a whole new lexicon of legalistic definitions and jargonistic initials. They introduced chaos where there had been only confusion.

If aspirin were to be submitted today for FDA approval the producer would have to submit to considerable preliminary investigations and three phases of testing before he could market his drug. Some authorities say that under current regulations aspirin would never make it to the drugstore counter.

First of all, the producer would have to apply for an IND (Investigational New Drug Exemption) permit from one of the many FDA bureaus (heart and kidney, metabolism and hormone, cancer and radiation drugs, nerves, dental, anti-infection, etc.). Because aspirin is used in something like thirty-eight fairly well defined situations, a good deal of time would be spent determining which and how many bureaus would have jurisdiction over the testing. The filing in triplicate of an IND usually qualifies the drug to be shipped (for laboratory studies) in interstate commerce.

Aspirin undoubtedly would be denied the privileges that go with filing of an IND; its widespread prior use as a cure-all for headaches, rheumatoid arthritis and many other conditions would have put it in what the FDA calls a controversial

status—along with hallucinogenic LSD and panacean DMSO, the two taboos of the 1960–70's.

If aspirin eventually received the blessings of three men from each of the bureaus—a medical FDA officer, pharmacologist and chemist—permission to test aspirin in humans could reasonably be expected. Chances are the FDA would be aghast at the lack of controlled studies in animals and humans, however, and it would withhold permission.

Highly trained clinical pharmacologists, armed with bushels of data accumulated in test-tube and animal studies, would then seek to trace any deleterious effects aspirin might have had on humans. They and the doctors who aided them could determine the toxic effects on organs and systems, how it is metabolized, absorbed and eliminated, what happens to it after various routes of administration (by mouth, vein, artery, etc.), safe dosage, and the like.

If aspirin passed inspection by one or a few pharmacologists, it would be graduated to Phase II and a larger number of patients, ideally paired for age, sex, disease, pregnancy or not, and similar criteria. It would be given to four species in massive doses by various routes to determine its acute toxicity and to two species (rodent and non-rodent, usually rat and dog) for two to four weeks to indicate subacute toxicity and its effect on certain enzyme systems, other body chemistry and blood composition.

Phase II, by procedures difficult to understand, might show whether the drug will impair the female's ability to reproduce or, if she be pregnant, will abort her or cause her to bear a deformed or mutilated baby. As Giambalvo put it, "In the early stages of human studies, teratology and reproduction studies may be temporarily postponed by using only institutionalized female patients and/or women with not a ghost of a chance of becoming pregnant."

Then comes Phase III, the final test—one which hopefully will show whether the drug really helps the patient. Efficacy, it is called.

Phase III calls for the elimination of patients who respond to sugar pills and other placebos, for double blind studies in which neither patient nor doctor knows who gets the drug and who the placebo, for the elimination of the physician's bias (enthusiasm or dislike for particular drugs); it requires consideration of concomitant therapies and the grading of pain.

If aspirin survives Phase III and the New Drug Application stage, it goes on the market—but only under the watchful eyes of the Office of Drug Surveillance, which reviews adverse reactions and the effects of supplements, and the Office of Medical Review, which monitors medical advertising, medical devices, and over-the-counter drugs and helps out on the FDA's legal problems.

Actually, its acceptability would be doubtful, because aspirin has produced large liver tumors in rats, appeared to deplete human blood and tissue levels of vitamin C, and induced hemorrhage and other untoward side effects in adults with peptic ulcers. Some report that it exerts a "rebound effect" of clotting, with implied risks of strokes and heart attacks. Aspirin kills more than 100 Americans, mostly inquisitive children, each year.

Under literal application of the law, any doctor who tells a patient, "Take a couple of aspirin, and if you don't feel better in the morning, call me," risks a malpractice action.

Despite the law, aspirin is freely dispensed over the counter to anyone who can pay for it.

In some respects, Edward E. Rosenbaum, M.D., was the antithesis of Jacob. Now in private practice, Rosenbaum had been Clinical Professor of Medicine and founder of the Department of Rhematology at the University of Oregon Medical School, a one-time intern in metabolic diseases at Michael Reese Hospital in Chicago, and, before and after his World War II service in the Army Medical Corps, a Fellow in Medicine at the Mayo Clinic. Rosenbaum was a broadly experienced, busy and prosperous physician.

Stocky, balding, middle-aged, Rosenbaum had a reputation in Portland as a hard-headed, feet-on-the-ground, show-me kind of doctor. He took nothing for granted, including patients' guesses and other doctors' diagnoses.

Rosenbaum had tested several new drugs for pharmaceutical houses and through his exacting requirements for evidence of safety and efficacy, had earned a reputation as being endowed with that precious scientific commodity, skepticism. it was this more than any other quality that made Stanley Jacob want to meet him and, if it proved feasible, work with him.

Jacob called Rosenbaum one October morning in 1963 and asked if he'd stop at his laboratory; he had a problem to talk over.

"I had a busy afternoon scheduled," Rosenbaum recalled. "I never will know why I canceled all appointments."

Rosenbaum had met Jacob only once or twice, and casually—Jacob had transplanted goat glands into one of his hypoparathyroid patients. Rosenbaum had heard rumors about DMSO, but he paid no attention to such patent fantasy.

Now Rosenbaum sat in a hard, straight-backed chair amid the swirl of laboratory smells and fixed Jacob with a shrewd clinical eye. He was wondering how the honored surgeon and scientist came by his glittering reputation.

Jacob held up a bottle of fluid. "You dab a little of this DMSO on the skin overlying the trouble," Jacob was saying, "and often within minutes the trouble vanishes. The headache disappears; sinuses clear; bruised tissues lose their ugly appearance; soreness leaves joints; pinkeye improves; bursitis subsides; many arthritics are helped.

"In less than one year of experiments, we've established multiple pharmacologic activities of DMSO." Jacob ticked them off on his fingers: "Analgesia, anti-inflammation, bacteriostasis, diuresis, tranquilizer, membrane penetration, transport and enhancement of other drugs, collagen solvent, non-specific immunity stimulant, and vasodilation."

When Rosenbaum gave no response, Jacob asked, "What do you think?"

"I think," Rosenbaum could have said, "that if you were my patient, I'd order you away for a long rest." Instead, he went to the door and closed it, and exhorted Jacob, "Look, Stan, you are secure now. You've got a good job. You've got prestige. Nothing's going to happen to you. But you're rocking the boat. Why don't you forget DMSO? Otherwise, you might destroy yourself and wind up without a job." Jacob's unhesitating response was, "Nothing doing."

This was the beginning of an all-weather research association.

Rosenbaum's initial experiences with DMSO were far from reassuring. His wife had a pain at the base of the thumb; DMSO didn't help. He tried it on a couple of other minor conditions. It was no good. Jacob had speculated that it might

dissolve insulin and transport it through the skin, thus ending the need for insulin injections for diabetics. Rosenbaum promptly added insulin to DMSO and applied the product to his and Jacob's arms; it did not affect their blood sugar.

Jacob called Rosenbaum three or four or six times a day to inquire, "Have you used the DMSO? Have you seen anything yet?" One one occasion, Rosenbaum said, "Stanley, I have three arthritis patients in the office. They're willing to try DMSO. I'll keep them here for you." Jacob rushed down to Rosenbaum's office and applied the DMSO to the knees of the elderly women.

Within minutes of treatment, each of the patients professed to being free of pain—miraculously.

Jacob glowed.

Rosenbaum glowered. "I don't believe it," he said.

The next day Rosenbaum called the patients, and each confessed that she had not been helped at all. Furthermore, the DMSO had not given them a single moment's release from pain. Why had they lied? Each said approximately the same thing: "He was such a wonderful, earnest young doctor. I did not want to hurt his feelings."

Cynic, skeptic, doubter—whatever else Rosenbaum was, he was also tolerant and tenacious. He was convinced of one thing: DMSO did penetrate the skin—he had smelled it on his patients' breath. He also felt that Jacob was highly intelligent and utterly honest.

The two men met daily at lunch and talked DMSO. Jacob continued to call frequently to ask, "Ed, have you seen anything yet?"

A month or so after their first meeting, Rosenbaum said, "Look, Stan, I have yet to see one hopeful sign. Let's try it once more—in the rheumatology clinic at the medical school."

This was the clinic Rosenbaum had founded eleven years earlier and had headed up until he went into private practice three or four years ago. They went to the clinic that after-

noon, selected a woman patient, explained the proposition and obtained her ready consent to the experiment. They gave the patient a small bottle of DMSO and instructed her in its use.

It occurred to the two physicians that, as a matter of courtesy, they should advise the chief of the clinic—Rosenbaum's successor—of their program.

At this point Rosenbaum entered the gates of the hell in which Jacob had resided since shortly after tasting and testing DMSO.

"The chief of the clinic was very angry," Rosenbaum later told me. "He said DMSO was worthless in any rheumatic disease—our trials would bring disgrace upon his clinic—he would not permit us to use it."

They were made unwelcome at the clinic Rosenbaum had built.

When things looked blackest to Rosenbaum, he felt impelled to call Dean Baird and suggest that he reprimand Jacob—to save Baird from further embarrassment and Jacob from utter disgrace.

It was the first time Rosenbaum had ever called the dean.

"There's quite a stir at the school about DMSO," Rosenbaum finally blurted.

"Nobody believes Jacob," said the dean. "What do you think?"

Until this day, Rosenbaum doesn't know why he changed his course at that moment. Instead of warning Baird about Jacob, he heard himself saying, "I admire you for permitting him to go on with what appear to be negative results."

The dean laughed and hung up. Not many were tolerant of Jacob on the medical school campus.

On December 24, Christmas Eve, 1963, as Rosenbaum was closing his otherwise deserted office, a patient walked in with bursitis so painful that he could not move his shoulder. He had been unable to sleep the night before. Rosenbaum had him strip, examined him, and x-rayed his shoulder. He told

the patient he had a new drug of unknown toxicity which might help. The patient begged him to try it.

Rosenbaum painted a small amount of DMSO on the man's shoulder and sat down and talked to him. He watched with some concern as the painted skin became red and itchy; and he could smell the typical oder on the patient's skin and breath.

"After fifteen or twenty minutes, the patient looked at me and started to laugh," Rosenbaum told me. "He said, 'I can't believe it; the pain is gone.' I couldn't believe it either. I told him it probably was mere coincidence. I gave him a prescription for codeine and told him that if he had trouble, be sure and call me. He called me the next morning—Christmas Day. He told me he was almost free of pain.

"During the next two months, four more patients came to me with acute bursitis. Each was cured—I detest the word, but it almost applies—miraculously."

It was Rosenbaum's turn to do some telephoning. He caught Jacob just as he was leaving for a meeting in Florida. "Go in peace," Rosenbaum said. "Even I believe you have something."

Rosenbaum called Dr. Norman David, Head of the Department of Pharmacology, and at David's suggestion called the dean that evening at home. "I thought I heard a great sigh of relief, when I told him that DMSO was beginning to look good."

Ed Rosenbaum had earned his skepticism the hard way—by finding serious faults in the lessons learned at medical school, by discovering that the dogma and adages of his profession could be dreadfully wrong on occasion, that believing the clichés could lead to disaster, that the procedures and preparations considered safe and conservative in one edition of the medical manuals might be found dangerous and deadly in the next.

In 1952, Rosenbaum had the impression that chloroquine,

the antimalarial, had helped his rheumatic patients. "Never trust clinical impressions," he reminded himself. For two years he and his associates conducted meticulous double-blind tests, and the data supported his observation handsomely. The facts and figures were pulled together in a carefully worded article and sent off to a journal. Before it was published, several other investigators were in print with sketchy data but the same conclusions. Credit to Rosenbaum et al., went down the drain.

Rosenbaum trusts no drug. Nor does he find implications in animal experiments very persuasive. Salvarsan and digitalis, he points out, are eminently safe in some laboratory animals in doses that would be a multiple of the lethal dose for humans; and Chloromycetin, which passed all lab tests and appeared safe in humans, was found to kill one in 68,000—a very lethal rate if you happen to be that susceptible person.

"It is often terribly hard to detect toxicity," Rosenbaum once told me. "A common assumption that if animals can survive a strong dose of Drug X, humans can take a small one, can be fatal reasoning.

"From the point of conception, we face one near disaster after another. We face risks during residence in the womb, during our passage through the birth canal, walking across the street, or riding to the moon. In using drugs we must weight the potential risks against the possible advantages. It makes a difference whether we are seeking relief of a minor pain or treating cancer."

DMSO in short order shattered a few more of Rosenbaum's idols.

A pharmacist friend had bothersome bursitis. Rosenbaum gave him a bottle of DMSO and told him to use it. The next morning the patient's wife called and said that for a while she had thought her husband had died—he had slept fourteen hours without stirring. It was his first sleep in many nights.

The pharmacist, however, said he wasn't at all sure that DMSO deserved credit for the improvement.

One of the severest critics of Rosenbaum and Jacob borrowed DMSO and applied it to the bursitic shoulder of his policeman patient who was beyond other help. Within a half-hour the patient was almost pain-free. "What do you think happened?" Rosenbaum asked.

"There's no doubt about it," his critic said. "This case quite obviously has been misdiagnosed; whatever the condition, there has been a spontaneous remission." That point having been resolved, the physician asked earnestly: "Do you think I should buy Crown Zellerbach stock?"

An important professor came into Rosenbaum's office with a fresh bursitis of the shoulder. He said, "When I had an attack four years ago, the pain didn't respond even to morphine. The pain is back. I couldn't sleep last night, although I took large doses of codeine. I'm telling you now I don't believe what you and your fellow enthusiasts say about DMSO. But go ahead and try it on my shoulder anyway. I have nothing to lose." Terrified by the challenge of testing DMSO on so eminent and hostile a patient, Rosenbaum painted the shoulder with DMSO.

"He got the itch, the rash, the taste in his mouth," Rosenbaum recalled. "But while he was in my office, he couldn't be sure that he received any relief from pain." Rosenbaum gave him DMSO, told him to apply it every four hours if he could stand it, and sent him home. "He came back the next morning laughing. He told me it had worked."

Rosenbaum learned that patients, like drugs, should not be taken for granted.

Jacob faced the dilemma that confronts every scientist who has made a major discovery: When is the right time to claim credit? Unseemly haste could incite professional contempt. Delay could result in the glory going to a plagiarist.

There is a good deal of truth to the sardonic slogan: Publish or perish! Unless one gets something—almost anything—in the journals with reasonable regularity, he stands to lose face among his immediate superiors and associates, prestige in his field, and support from the granting agencies.

Scientific and medical journals do not pay their contributors for articles. On the contrary, authors pay for reprints. And considering the quality of the articles, this is as it should be 90 per cent of the time.

For their services, most editors earn only whatever honors accrue from having their names on the masthead. And this too is as it should be; it makes clear where the blame belongs.

Scientists, doctors—and let us not forget, engineers and educators—have managed to construct awkward, pompous jargons which not only are unintelligible to the unwashed public but sometimes beyond the understanding of the inventors as well, a counfounding curse of tongues, a cryptographic code lacking a key. The archaic, anti-semantic prose, the pretentious Greco-Latin hybrid terms, the obfuscatory, pseudo-modest passive voice, the tedious and meaningless technical detail, the open bridges in logic, the

anachronisms, the ambiguities and obscurantism in data, the craven "it is tempting to conclude" sort of non-conclusion, and the timid "may warrant further investigation" copout—all these contribute to the illiteracy of the professions. One survey showed that the average doctor reads fewer than three journals a month. Scientists glance through more publications than that, and some of the articles, they may actually read. By and large, however, the 14–25,000 or so medical and scientific journals represent a modern monument to the Tower of Babel.

Journals sometimes refuse to publish articles because the material is too new or too explosively significant. Many of the great scientists have found it difficult or impossible to find an outlet for some of their most challenging papers. The young and relatively unknown, especially, have been denied credit, in this wise, for work that others repeated and reported and sometimes won awards for years later.

Besides their journals, scientists have one other medium of communication—the professional meeting. This event comes in many sizes. There are small get-togethers of between ten and a hundred scientists or physicians who gather in an isolated but comfortable resort to mull over a medical or scientific problem for several days. Usually, the speakers know each other well; they have spoken and listened to one another for years; sometimes any one of them can recite, without notes or prompting, what any or all of the others can be expected to say.

There are large conventions where one or two or three thousand papers will be droned out before numerous scattered audiences of mostly bored people who don't hear, or understand, or care what is said and who are too beaten to protest against the illegible tables and the meaningless charts and graphs shown on the screen.

The most mature and candid will confess that the meetings

have come to depress them, that they are an ill-afforded drain on time better spent in their laboratories.

There are exceptions to the foregoing. A few scientists and physicians do a creditable job of educating others. Their papers are clear, erudite, significant, stimulating. Their lectures awaken an audience and send them away with new ideas, new zest, new means and methods of exploring new areas. And, in some, a sense of outrage.

Gifted with total recall of facts that he considered solid and significant, remembering precisely where to look for data published by others, knowing exactly what he wanted to say and how to say it so that it could be understood easily, Jacob found neither lecturing nor writing a great chore. He could dictate in a couple of hours a first-rate paper for which some scientists would take a month or two off to write badly. Before he had heard of DMSO, he had published about forty papers in prestigious journals, most of which had attracted considerable attention. He was to become the author of medical books that sold widely.

Jacob's lectures were lucid, his critiques incisive. A one-time champion debater, he was a formidable foe where facts were at issue and he was skilled in taking specious arguments and fatuous orators apart.

Jacob had one great failing, however, he was unable to lie or dissemble or equivocate. Even to newsmen. For this weakness, which, as it turned out, was unpardonable in his profession, he was to pay dearly.

Portland is fortunate in having two highly competent medical and science writers—Marge Davenport of the *Oregon Journal*, a youthful mother of five youngsters, and Ann Sullivan, of the *Oregonian*, a mature, attractive brunette of the old aggressive school of journalism. Both writers heard the first rumors about DMSO; they checked then with Jacob, who told them the truth; and although they were keen com-

petitors, they refrained from breaking the story, because premature publication would embarrass Jacob before that large professional conglomerate known as his "peers." They were holding back a medical matter of high journalistic and public interest; but they did so long after Portland physicians had noised the news abroad and were buying Crown Zellerbach stock.

Jacob's housekeeper told the reporters that after she had had her swollen and painful jaw painted with DMSO, following extraction of several teeth, symptoms of an old stroke improved; her uncertain gait became steady; she could take a pen in her paralyzed hand and write.

Agricultural researchers along the Hood River had shown Miss Sullivan apple trees which had been withered and old; a shot of DMSO into the growing, juicy cambial layer, just under the bark, made them suddenly lush with leaves and with other signs of youth.

Miss Sullivan's octogenarian baby-sitter fell and injured her thumb and wrist. Ann told me, "We put some DMSO on that big, green, pulsating hand, and, as we watched, the swelling and pain left." She said the UCLA football team used DMSO liberally—"They won the conference championship, and some of the team lost their girls because of the DMSO odor."

"Stanley is a generous man who lives only for others," Miss Sullivan said. "He has not the slightest desire for money.

"He is the complete genius. He can turn off all his personal troubles and give himself completely to what he feels must be done for others. In this case, DMSO had to be made available to sick and suffering people. His motive is that simple.

"He likes women. He is adored by the nurses. It is possible that his appeal to women may account for the bitterness of his male critics. It could be biological.

"He is hard-driving and unhappy. He has no hobbies, no

sports. He has no time to play. At parties, he'll toy with a drink for a while and then take off. When he comes to dinner, he eats, sits on the davenport, falls asleep, gets up and goes home—or, more often, back to the lab.

"He doesn't spend money on himself. He has no possessions. He doesn't care about cars, or clothes, but he wears his clothes well and he is handsome. He doesn't dislike anyone. And he just can't understand why anyone would dislike him."

The day came when Marge Davenport and Ann Sullivan had to release the story. By all the practices of good journalism, by whatever code might be involved, by all the tenets of human communication, common decency and common sense, they had to print the facts. They explained this to Jacob; and, while he would have liked to appease his critics by holding off until the facts were published in a scientific journal, he realized that the choice was not his or the reporters'.

The precipitating circumstance was the filing of a contract in Salem, the state capital. In this public document, which was available not only to the press but to any man, woman or child who cared to see it, Crown Zellerbach and the state of Oregon, through its Board of Higher Education, became partners in the patented medical uses of DMSO. The patents actually were requested for Herschler and Jacob as representing their respective institutions. The formal document described the major uses to which DMSO had been put, and the information became public property from that moment.

Portland newspapers carried the story on page one on December 10, 1963. But for all the excitement it stirred outside Oregon, it could have been buried "back among the truss ads," as they say. The wire services brushed it off with a perfunctory couple of paragraphs, which many papers ignored completely. The *Oregonian* later carried an editorial

bewailing the effete Eastern attitude toward earthshaking news originating in Indian Country.

Then, on Wednesday, December 18, the *New York Times* gave the story its seal of approval. It played on page one Robert K. Plumb's piece about DMSO's "creating a stir in medical circles in Portland." That was all that was needed.

Crown Zellerback stock jumped $5.50 a share that day to $60.25. *Newsweek*'s medical editor, Matt Clark, contributed a lucid account in the issue of December 23. *U.S. News & World Report* followed on December 30 with an article on the testing of "a drug that could open up a new era in medicine." *Life* and *Saturday Evening Post* writers began looking into the story for future spectaculars.

Then, for almost two years, articles were frequent in almost all major publications in the United States and in many abroad.

None of the principals—Jacob, Rosenbaum, the university, and, certainly, neither Herschler nor Crown Zellerbach—was happy about the publicity. (Crown stock quotations had fallen back to normal when the corporation pointed out that DMSO could not amount to more than a drop in its corporate bucket.) Everyone involved wished that the press could and would have held off until the DMSO story could be obtained from medical and scientific journals.

To set the record straight, it must be said that:

1) The first written accounts of DMSO as a drug were submitted to medical journals between four and six months before the news broke in the public press; and

2) The first oral description was delivered to scientific audiences more than two months prior to the news break.

In all instances, nobody in authority believed that a compound with DMSO's versatile biological activity could possibly exist. The situation was not new. Doubt of this sort had delayed major scientific effort since before Galileo.

During the summer of 1963, Jacob and Herschler had written a paper on the basic pharmacology of DMSO and sent it, in turn, to *Science*, *Nature* and *Surgery*. All of them said no, thanks. Obviously, they regarded as preposterous the claim that the authors had discovered seven primary biological actions in one very simple solvent.

In October 1963, Jacob presented his report before the Surgical Biology Club, which meets each year just prior to the annual meeting of the American College of Surgeons. The members listened to his lecture with interest—and amusement. Many thought he was ribbing them; and they shook their heads and chuckled at this rare brand of humor. He offered to report to the Society of University Surgeons; they turned him down.

In effect, the efforts to publish eventually became a hectic, last-ditch search for cover. Patents for DMSO medical uses had been applied for and the partnership papers, joining the Oregon Board of Higher Education and Crown Zellerbach, had been drawn up and had to become public before the year's end. In the race against time, Jacob, along with his friends and associates, had run a poor second.

Jacob and all who were associated with him breathed a little more easily when it looked as though DMSO would qualify for "respectability." Arrangements finally were made for oral presentation before "peers" and also for the drug's debut in formal medical and scientific literature.

Jacob reported on the pharmacology of DMSO before the faculty of the University of Oregon Medical School. There never had been so unruly a session in the history of the institution. The auditorium was hot with the heat of more than 100 keyed-up faculty members. Plus a few research assistants and students, all of them solidly in the seats, aisles and all open spaces. The questions were leading and pointed, like switchblades. Tempers flared. Some were heard to cry out, "Liar!" "Quack!" "Charlatan!" It was Jacob's first intellectual mugging.

A day or so later, Dunphy, the Chief of Surgery, summoned Jacob into his office and told him that a few faculty members had asked Dean Baird to fire Jacob. Dunphy was upset and embarrassed; but inasmuch as he was about to leave for a job at the University of California Medical School in San Francisco, he did not pursue the point. The friendship, which dated back to Jacob's residency at Harvard, survived.

Jacob, Margaret Bischel (a senior medical student) and Herschler submitted an aritcle on "DMSO: A New Concept in Pharmacotherapy" to *Current Therapeutic Research*, a

journal of limited circulation. The article appeared early in 1964 over an editorial apology: "The above serves to record a most unusual series of biological responses to a widely known compound which has not been previously used as a medicinal agent. The authors give assurance that several colleagues are currently assembling the data on their clinical observations for publication at an early date." It was only because Dr. Norman David, a sympathetic associate editor, had intervened, that the piece ever saw the light of day.

Another article, by Jacob and Rosenbaum, on the first seven patients treated for bursitis, was submitted in January and appeared in *Northwest Medicine* in March 1964, and still another on DMSO and arthritis in the April issue. *Northwest Medicine*, a readable and informative journal, has as its editor Herbert L. Hartley, M.D., who likes to have solid reasons for accepting an article and equally valid grounds for rejecting one. He knows most of his contributors personally—those he publishes and those he rejects—and it is very hard to find a literate and reasonable doctor in the Pacific Northwest who doesn't swear by Herb Hartley and *Northwest Medicine*.

The legitimization of DMSO—if articles in two professional journals could be called that—was a mixed bag. It opened the floodgates of powerful prose for the news media. Instead of appeasing the critics, professional publication seemed to embitter them more; one young Ph.D. dropped into Jacob's lab one morning only long enough to say, "I have come all the way from the state of Florida to see the author of the most preposterous paper which has ever appeared in the medical literature."

Professional publication set off a scramble among doctors everywhere for some of this precious stuff, DMSO, and while many of them used it with common sense and caution, others initiated an epidemic of wild, senseless, irrational experimentation on humans. Some experimentalists lacked the scientific background to treat white mice.

Dr. H. P. Dygert, a part-time faculty member, could have spoken for most, if not all, the dissident elements at the medical school in deploring "the unforgivably unscientific manner in which the investigation has been carried out or the publicity offered." In a letter to the editor of *Northwest Medicine,* he said, "The inherent dangers in this situation, both legal and in the potential harm to medicine's position of leadership in health matters in this country, should our position be challenged, is uncalculable." He ended his reprimand with a cryptic observation in classical medical journalese: "I urge all persons in a position to influence this situation, and particularly the University of Oregon School of Medicine, to review this entire matter and to attempt as rapidly as possible to bring it into proper perspective."

Dygert protested that one of his patients with obstructive emphysema and ulcerative colitis had asked for DMSO treatment and had been accepted "until I intervened."

DMSO, an investigative drug, was distributed in 1964 under the name Dymasol. Zirin Corporation, in offering it for "fantastic relief, almost instantly, from most of the time and money-losing aches and pains of horses," quoted liberally from newspapers and magazines and acclaimed DMSO as "one of the most important medical events of the century—comparable to the discoveries of penicillin, insulin, and the life-saving vaccines."

"This epoch-making drug is unique in so many ways that it would require a substantial volume to detail them—it is probably the first drug administered to more human beings than to animals for clinical investigation," the ad said.

Those who knew DMSO best might have agreed with all or a good deal of the advertising. But they winced, nevertheless. The hard sell pitch did not help the cause of DMSO. Or of Jacob, who was being battered by other problems, and who was relieved when Dymasol was withdrawn.

Some faculty members who formerly smiled greetings now would nod curtly or look away as they passed Jacob in the hallways. Itinerant colleagues were damning his findings as having no validity.

Whereas, until DMSO, Jacob had been elected to learned societies and professional organizations with unanimous and enthusiastic endorsement, he now ceased getting invitations to join. Twice he had been proposed for membership in the Pacific Coast Surgical Society, and twice, after bitter fighting, under charges of quackery and charlatanism, he was rejected. At the third meeting, he was accepted; his champions—Dr. Clare Peterson and Dr. William Krippaehne, surgeon friends and associates at the medical school—launched a counterattack which made a narrow majority of the members vote him in.

Jacob's opposition here came exclusively from downtown surgeons, many of them with quite ordinary academic credentials. (Jacob had and has no enemies in his own department of surgery.)

By way of contrast, Jacob had been given the largest number of votes of any candidate the year he was elected to the Society of University Surgeons, strictly major league; but that was in 1962, before anyone knew of his interest in DMSO.

Jacob was elected also to the Surgical Biology Club, an

elite group of fellows of the American College of Surgeons; he was one of only two or three who were not departmental chairmen. This appointment took place in 1960—two years before DMSO—and was on the basis of his status not so much as a surgeon but as a scientist.

About the only other group Jacob wanted to join for reasons of professional prestige was the American Surgical Association. He gave up hope when he learned of the bitterness of the Pacific Coast Surgical Society members.

He soon noticed coolness even among some old acquaintances at the meetings of the American College of Surgeons, in which he had been enrolled in 1960. The ACS is large, authoritative, progressive and responsible. As in all professional societies, there is an element of politics in the election of its leaders, and, consequently, the quality of its service varies somewhat from one administration to the next; but, by and large, the college tries to fulfill its obligations to the public as well as to its members.

At this time, with a few faculty members imploring Dean Baird to get rid of Jacob "for the good of the school," Jacob sent a report on DMSO to Dunphy, his friend and immediate superior. He had treated some patients with precarious conditions—he listed a score of them—and, seemingly, with good or excellent response. Dunphy sent Jacob a note saying, "This smacks of Andrew Ivy." (Dr. Ivy was the prominent educator at the University of Illinois Medical School who was then supporting Krebiozen, a controversial cancer drug.)

"Dr. Dunphy didn't want to hurt me," Jacob explained. "I think he was trying to save me. He was the one who arranged for me to write my book *Structure and Function in Man*.

"At about this time, Dr. Dunphy said at one luncheon meeting—and I'll never forget it, because it was so unusual—that he had had a dream that the DMSO matter had been turned over to the National Academy of Sciences."

Inasmuch as that was more than eight years before the

National Academy did agree to look into the DMSO matter, Dunphy's experience may have been more a vision than a dream.

Until DMSO, Stanley Jacob was buttonholed regularly at large medical meetings to accept positions at other medical centers. That was between 1959 and 1963. For the next decade, he was not approached to take work elsewhere.

Periodically, research advisory committees meet to study scientists' applications—like Jacob's—for grants, to discuss them, and to render a grade and an opinion on each of them for the benefit of the government or voluntary agency being solicited for support. The committees or councils are composed of panels, each of a dozen or so reputable scientists who consider projects within or akin to their speciality. The committee members serve as a favor to science generally and to the agency, and they receive only their out-of-pocket expenses for their day or two in New York or Washington. A fringe benefit quite often is that the panel members themselves have grant applications to be debated by the committee (they absent themselves for a few minutes during this discussion); and they are in a position to say a good word for a friend or a sour one for an enemy.

Some feel that a scientist could be a rapist, a drunk, a child molester, or a devotee of plain and fancy perversion and still receive his grant if he avoids professional flamboyance. This is most adroitly done by publishing a great many wordy and highly technical papers about insignificant work. Whenever a project reaches the point where it is about to produce a cure for a serious disease, however, the grant is in jeopardy; it may not be renewed. The most sophisticated practitioners of grantsmanship do not publish or advise committees of an earthshaking development in their studies until later, when they have under way a new project of a more or less bland, amorphous nature.

Advisory committee members, or the granting agency's

employees, draw upon a strange lexicon to damn a scientist or a project that is not to their liking. "He is very enthusiastic about this," is a surefire way of condemning an application. Or, "Oh, yes, I read articles in the newspapers about this work." Or, "Good man, Jones, brimming over with new ideas. Very imaginative fellow."

Stanley Jacob had worked on a lot of grants from an assortment of government and other agencies. He had no trouble getting grants, despite the fact that he was honest, unable to dissemble, and, you should excuse the expression, enthusiastic. None of his studies posed any immediate threat to the solid structure of conventional medicine. There were implications but not immediate applications in nerve resection for peptic ulcer, hormones for hemorrhagic shock and kidney transplants, enzyme activity in pancreatitis and in various surgical emergencies, the removal of lobes of the liver, bone marrow transplants to overcome lethal x-rays, the super-cooling of hearts and other organs for transplantation, the effect of body cooling (in surgery) on the brain, and stomach freezing for ulcers. None of these studies yet had reached the stage where doctors were confronted with the prospect of having to learn new practices in medicine; that came later.

Then came the DMSO. Grants that Jacob had obtained without effort became hard to get.

The year 1964 had its sweet as well as sour seasons.

Jacob made extraordinary progress in extending his clinical trials with DMSO to such challenging areas as nerve blindness, baldness, various infections, gangrene from several causes, disc troubles, diseases of the digestive tract from glossitis to hemorrhoiditis, from psoriasis of the scalp to athlete's foot, and disturbances stemming from all the external and internal organs.

Jacob began his clinical experiments gingerly; but as animal work indicated that basic biological safety of DMSO and his clinical observations showed it to be a drug probably without parallel for both safety and efficacy in an amazing number of conditions, he became emboldened. He tested the solvent's mysterious powers against fearsome ailments considered difficult or impossible to treat effectively.

At this time the officials of the Food and Drug Administration were encouraging and co-operative. On March 18, 1964, FDA, Crown and University of Oregon representatives met in Room 2029 of the FDA Building back East. Present for the FDA were Drs. Frances O. Kelsey, G. W. Schepers (pathologist), E. I. Goldenthal (pharmacologist), and J. A. Kaiser (also pharmacology); for Crown, Dr. W. M. Hearon, two lawyers, Vincent Kleinfeld and Richard Nelson, and Bob Herschler; for the medical school, Drs. Jacob and Norman David.

"The FDA representatives seemed anxious to do everything possible to permit further testing of DMSO," Jacob told me later. "They pointed out that DMSO was a very versatile drug; and because of this they were a little apprehensive as to how many IND applications might be filed to test not only DMSO alone but DMSO in combination with various other pharmacologically active substances.

"Dr. Kelsey said the number of combinations could be a hundred or more, representing a formidable challenge for a bureau that already was overburdened."

David produced more than 100 pages of toxicological data on DMSO which had been compiled by medical school investigators; and Jacob reviewed his methods of application, dosages and results, most of them necessarily of a preliminary nature.

Jacob described clinical trials at Oregon State Hospital in which mental patients were being given about a teaspoonful of DMSO orally every day. Although members of the staff had themselves taken this dosage for some time and had administered DMSO orally in large doses to animals without serious reaction, the FDA officials said these experiments must cease because there were not sufficient animal data to warrant them.

"Dr. Kelsey and her group seemed almost apologetic," Jacob said, "and they expressed the hope that the work would be continued since the goals were obviously worthwhile. Dr. Schepers said we could start our clinical testing again at Oregon State Hospital as soon as we had one month's toxicity data. He suggested running a series of dogs on a one-administration-a-day basis for only one month, autopsying a dog each month, and, if no abnormalities occurred, obtaining a permit from the FDA to start again the study at the hospital."

At this point, the FDA could not have been more reasonable. And, consequently or coincidentally, science and medicine in the United States were in fairly healthy shape.

Even during this period of peace, however, the FDA was responding to pressures from politicians in Congress and ambitious officers within its own structure. Publicity and power were to be had in assuring the public that thalidomide-type disasters would not happen here. They were right. But another kind of calamity could have been building up as an overreaction to a danger which had passed.

The drug houses became skeptical, then curious about DMSO and, finally, interested. There were mixed feelings; DMSO had to be an inexpensive product and, if it lived up to its early promise, it could substitute for a large number of pharmaceuticals which had cost the drug houses vast sums to develop and now were costing the public a lot of money to consume.

It fell to Ed Rosenbaum to handle the greater part of transactions. He had tested several new preparations for pharmaceutical companies; he knew their officers and clinical advisors; he knew their psychology, their habits, their language. And under Rosenbaum's guidance, drug house enthusiasm for DMSO rose—and so did drug house investments in expensive laboratory and clinical testing. As the FDA's demands on DMSO became more stringent, the costs of testing rose to $10 million, then to $15 million and beyond. If and when DMSO is every marketed, it may represent one of the industry's most investigated and invested-in drugs.

Rosenbaum told me later of episodes during those turbulent times.

Crown's executives invited him and Jacob to lunch occasionally.

"I was impressed with their total ignorance in the field of drug evaluation," he said. "They seemed to think they were dealing with an ordinary chemical compound and it could be handled as any other pulp or paper product.

"They were fine, pleasant men; but like all corporation

executives, they exhibited a great drive for profits. When things were going well, we were the greatest people in the world. Crown always gave us a free lunch and occasionally sent us a Christmas card.''

Rosenbaum applauded the care with which Crown selected drug houses to conduct clinical investigations. ''They were determined to pick the most ethical and reliable drug firms,'' he said.

Rosenbaum reported that after being courted by Geigy, he reccommended them for a license, but Geigy later became disenchanted with DMSO.

Ed called DMSO to the attention of Max Tishler, a dynamic figure in the pharaceutical industry, president of the Merck Institute and director of medical research. Merck assigned Dr. Richard Brobyn—young, sharp and knowledgeable enough to entertain enthusiasms—to investigate. Brobyn dug, felt that he had struck pay dirt, and reported accordingly.

Rosenbaum said Squibb was among the first to confirm the fact that DMSO would transport some drugs across tissue membranes. He didn't have much information about the role played by American Home Products.

Syntex showed considerable enthusiasm, for a while at least. They assigned Dr. Gerhard Boost, a former thoracic surgeon then in Salem, Oregon, and a man with a high sense of ethics, to undertake extensive clinical studies. It was Boost's feeling that any information which might preserve human life could not become a secret to be held in commercial trust indefinitely.

The American Schering Corporation undertook clinical studies under the direction of an able pediatrician, Dr. Sam Bukantz of St. Louis. The studies apparently ended abortively when Bukantz transferred to Hoffman-La Roche Corporation.

Jacob, meanwhile, had to cope not only with the angry

men in his audiences, the bitter critics on his campus and the journal editors but also with the massive, impersonal, immutable structure of medicine. Most of the disciples he won were unwilling to face the cold resistance, if not abuse, which impeded his own progress.

Beset by hostilities at home and disdain elsewhere, Jacob, nontheless, never lost his sense that DMSO someday would triumph. An endless succession of unexpected events dispelled any tendencies toward depression.

There was the time, for example, the Texas doctors had to play God. They had to decide whether to let the little black boy die decently and quickly or to risk heroic measures which might inflict disability or an ugly and painful death.

The boy, aged seven, had entered a hospital in great pain, his belly distended grotesquely with peritonitis. The surgeons opened him up, found the small intestine gangrenous and the large intestine twisted and completely blocked. They removed his digestive tract from just below the stomach to the mid-bowel. The operation didn't leave much intestinal surface through which ingested nutrients could pass into the bloodstream. And so—sick and slowly starving—he was moved to the pediatric services of Wilford Hall, Lackland Air Force Base Hospital, near San Antonio, Texas. It was just before the Yuletide; the spirit of the Magi may have prevailed. Death is not a fitting Christmas gift for a child.

Intravenous feeding of high caloric fluids and electrolytes failed to compensate for the diarrhea and malabsorption, nor did it stem the wasting of muscle, the progressive weight loss, the anemia—the deterioration of what had been a little boy.

When it became almost impossible to find veins for injections, three of the Air Force doctors—Lt. Col. Robert E. Smith, Capt. Andrew M. Hegre, Jr., and Capt. Clement N. Rieffel, Jr.—decided to undertake an experiment that some would have considered a journey into fantasy; they would try to feed the dying boy through his skin.

The doctors mixed a glucose solution with an equal amount of 100 per cent DMSO and swabbed it on the boy's skin. Gradually the stuff dissipated, and at the end of twenty minutes, serum tests showed, it was gone completely—into the lad's system. Then they added to DMSO some vitamins, fats, proteins, minerals; and he was "fed" dermally five or six "meals" a day.

It was touch and go, but during the first thirteen days on this regimen the boy's weight rose from 32.75 pounds to a glorious thirty-five pounds; and during the next week he added still another 1.25 pounds. At this point, however, his anemia became acute, his weight dropped to thirty-four pounds, and it was necessary to cut through the flesh to find a vein capable of being catheterized for injections of vitamin B_{12}, iron and other essentials. Once again, flesh began to fill out the bony outlines, and by July 5, he tipped the scales at a remarkable thirty-seven pounds. Then, on July 9, a slight but sudden rise in temperature indicated infection—possibly caused by the indwelling catheter—and on July 10 the catheter was removed.

The boy did well for the next few days. But on July 15 at 3 A.M., the hour when, some say, human resistance is at its lowest, his lungs became congested and his breathing labored. He went into a coma; and, despite desperate measures—including a feeding tube inserted into his jugular vein, antibiotics, transfusions, electrolytes, suctioning of his fluid-filled lungs, and other tactics—he quietly died on July 16. At 3 A.M..

The autopsy showed pneumonia the cause of death and "no evidence of toxicity from DMSO."

The doctors said their tests "left little doubt that the

nutrients crossed through the skin barrier in usable form''; but they added that the replacement of fluids and electrolytes remained a problem. ''Supplemental feeding through the skin with DMSO *does* seem possible,'' they concluded.

Jacob and Rosenbaum were invited by Dr. Gerhard Laudahn, Director of Schering AG, the German drug house, to a special one-day symposium on DMSO in Berlin in July 1965. Both men gratefully and hopefully accepted; they were pretty well worn out by the battles at home and thought that, even if the trip amounted to another series of conflicts, at least it might be refreshing to fight on foreign ground.

Berlin turned out to be a joy. They were met at the airport by Laudahn and Dr. Heinz John of Berlin, and they were shown the city and taken to Laudahn's home. They were guests of honor at the session; and, socially, they were given red-carpet hospitality.

Most gratifying of all was the intelligence and enthusiasm shown by the 150 German, Austrian, Scandinavian, Swiss and other European participants in the morning scientific and afternoon clinical sessions. Those who spoke did so from knowledge; those who asked questions were curious and courteous. None seemed disposed to argue for the sake of argument.

''The thing that impressed me,'' Rosenbaum said later, ''was that while the Germans started their DMSO studies later than American pharmaceutical houses did, they seemed to be ahead of us.''

Late in 1965, when things looked dark for DMSO, Dr. Charlotte Maddock walked into the laboratory of Dr. Morris Green at Children's Cancer Research Foundation in Boston.

''She was all excited,'' Green later told me. ''She had started some experiments on the P-1534 tumor many months earlier—and all animals treated with a DMSO combination were surviving in good shape.''

''P-1534'' originally had been a spontaneous leukemia in

mice. When it was implanted in muscle or under the skin, it grew locally, infiltrated promptly and killed the mouse in about fourteen days. When treated early, it responded pretty well to either of two drugs, 5-FU or actinomycin D. With DMSO/5-FU, some mice were not only cured but they also became immune to the tumor.

Green shared Maddock's excitement. Together they tested several other drug combinations against more experimental tumors, with and without DMSO. In almost all cases—there was an exception or two—the cure or the dramatic response depended on whether DMSO had been used in the combination. DMSO alone, however, was generally ineffective.

L-1210 leukemia, which kills the mouse in about eight days, takes twice as long to kill if a common anti-cancer drug, cytoxan, is used, but the preparation has to be shot into the belly cavity—intraperitoneally, as they say. The same result (15.3 days survival) was achieved with DMSO-cytoxan merely dabbed on the skin.

Significant results—generally on the order of doubling the survival of animals treated with DMSO plus any of such agents as 5-FU, CRI-3, cytoxan, thio-TEPA and 6-MP—were reported in such induced animal tumors as other leukemias, cancer of the connective tissue and bone, and melanoma, or "black cancer," of the pigment-producing cells of the skin.

As late as September 8, 1965, all seemed well. A freshet of facts from controlled studies was streaming into the computers of participating drug houses. More and more scientists were testing DMSO against plant pathology, mouse cancer, an array of diseases in laboratory animals, and a rapidly broadening range of conditions in man. Some biochemical rationales for DMSO's numerious biological activities were beginning to emerge; and, perhaps most important of all, DMSO was opening the inner and outer membranes of cells to expose life's great secrets that lay hidden behind them.

On September 8, Merck Sharp & Dohme Laboratories sent out to all investigators under their auspices an advisory memorandum on the emerging role of DMSO in experimental medicine. The prospects for the release of DMSO as a prescription drug looked very bright.

Here are some of the points made by Merck, as I have reduced them to capsule form:

INTRODUCTION

DMSO has been under investigation for over a year. This revised summary reflects the clinical experience of that time. It is intended as a guide for investigators in regard to indications for use, dosage, method of administration, etc., and it provides information concerning precautions and possible adverse reactions.

DMSO therapy is constantly changing. New indications are developing and techniques improving for some older indications.

Most aspects of the mode of action have not been explained. The major properties of DMSO are:

(1) Relief of pain of injured or inflamed tissue. High concentration of DMSO applied to a nerve will delay conduction and eventually produce a block, but this has not been demonstrated in humans.
(2) A mild anti-inflammatory agent in animals, even with large doses. It partially or completely blocks certain auto immune connective tissue reactions like Freund's Adjuvant Arthritis and PPLO Arthritis in rats.
(3) It passes through skin without producing significant damage—a unique property. Other small molecules can pass through skin with DMSO to achieve a high concentration at a local site without systemic effect and undesirable dose-related side effects. Absorption may vary from one individual to another.
(4) It inhibits the growth of a wide variety of organisms in 20–40 per cent concentration. It is bacteriocidal to some organisms. Clinically, we have not observed spread of infections when DMSO was applied. However, DMSO should be used with caution in disorders when infection is, or may be present.
(5) Solvent effect on collagen has been demonstrated in scleroderma.

CLINICAL INFORMATION

INDICATIONS FOR USE

At the present time the main areas of use seem to be in 1. Orthopedics, 2. Rheumatology, 3. Surgery, and 4. Dermatology.

I. Acute inflammatory or traumatic conditions: 1. Acute bursitis, 2. Acute low back strains, 3. Acute soft tissue injuries, 4. Acute neck strains, and 5. Burns.

II. Chronic conditions—Rheumatology: 1. Ostheoarthritis of a) knees, and b) small joints of hand, 2. Rheumatoid arthritis, 3. Scleroderma and other connective tissue diseases.

III. Surgery: 1. Thoracic, 2. Abdominal, 3. Rectal and Pelvic, and 4. Orthopedic.

IV. Dermatology: 1. Acne and 2. Psoriasis.

EXPERIENCE WITH DMSO IN SPECIFIC DISORDERS

The total clinical experience to date with DMSO supplied by the Merck Sharp & Dohme Research Laboratories involves approximately 4,000 patients. The duration of treatment has ranged from a single application to daily administration up to 18 months.

ACUTE BURSITIS—The largest clinical trials have been in this disorder. In the majority of patients, decreased pain and increased range of motion has been observed in about 30 to 60 minutes. Relief lasts 2 to 6 hours, and usually the intensity of pain is not as severe when it returns. 70 per cent and 90 per cent seem to work equally well. 70 per cent causes less skin reaction.

ACUTE LOW BACK STRAINS—Relief of pain and discomfort has been spectacular in some cases. Accurate diagnosis is essential. In the majority of patients decreased pain and

increased range of motion has been observed in 30–60 minutes.

ACUTE TRAUMATIC DISORDERS—Strains, sprains, contusions, athletic injuries, industrial injuries and other traumatic situations have usually responded quite dramatically to DMSO. DMSO has masked a few fractures, so x-ray diagnosis in most cases is advisable.

ACUTE NECK STRAINS (whiplash)—Wide area of application has given good results.

OSTEOARTHRITIS—DMSO applied to osteoarthritis of the knees has produced a favorable response after 4 to 6 weeks of daily administration. Transient relief may occur before this time. Increased mobility and general ability to walk and perform tasks without pain has been remarkable in some cases.

RHEUMATOID ARTHRITIS—DMSO seems less effective here than in certain other diseases. Grades 3 and 4 responded only partially after prolonged administration. DMSO probably would be an adjunct to other forms of therapy.

SCLERODERMA—DMSO has produced considerable softening of the skin and subcutaneous tissue and general improvement in a number of scleroderma patients. Almost all cases have shown some improvement. The concentration should be increased to 90 per cent or higher as skin tolerance increases.

BURNS—DMSO relieves pain in burns, including sunburn, in 10–30 minutes.

NEURALGIAS AND PAIN SYNDROMES—A wide variety of pain

syndromes have responded to DMSO. In tic douloureux, or trigeminal neuralgia, some but not all patients have obtained benefit. Treatment must be over a long time. The pain relief may not be permanent. Herpes Zoster has responded most favorably.

ISCHEMIC AND VARICOSE ULCERS—Some chronic ulcers that have not responded to other forms of therapy have improved with DMSO.

DUPUYTREN'S CONTRACTURE—Long-term administration has caused some improvement in fibrous scar contractures. 90 per cent is recommended.

PEYRONIE'S DISEASE—In a few patients so far treated, decreased size of the plaques and straightening of the penis has been noted.

REMOVAL OF CASTS—More rapid mobilization of joints that have been in casts has been observed.

THROMBOPHLEBITIS—Some pain relief when DMSO is applied over thrombosed vessels.

GOUT—There have been a few cases of dramatic relief of pain and general improvement.

VARICOSE VEINS—Relief of pain from varicose veins has been observed.

SINUSITIS—A dilute solution to the nasal mucosa has resulted in the discharge of a great deal of infected material from the sinuses and relief of pain.

SURGERY—After thoracotomies, cholecystectomies and

hemorrhoidectomies, 5 to 15 cc. dose 3–4 times/day, results have been very good.

ACNE—There have been some encouraging results. Long term administration has been necessary.

PSORIASIS—Pilot studies are underway. Results may be better with DMSO/Decadron than with DMSO alone. Long term therapy is necessary.

ADMINISTRATION AND DOSAGE

At the present time investigational use of DMSO is limited to cutaneous and mucous membrane administration.

DMSO should be used alone and not mixed with other drugs until toxicity studies with such mixtures have been completed.

DOSAGE—The volume of DMSO to be used in most disorders such as a shoulder or a knee is 8–10 cc., applied three times a day in acute and twice a day in chronic situations, with a cotton-tipped applicator or cotton ball.

The gel formulation, measured in a teaspoon or other suitable container, should be rubbed into the skin with the hand until a thin film results.

Small joints of the hand may be simply dipped into a solution, or it can be applied with an applicator or cotton ball.

Clothing should not be allowed to touch the area until the skin has dried for 30 to 40 minutes. One must be especially careful with synthetic fibers like Orlon and Rayon, since DMSO is a good solvent for these materials.

CONCENTRATIONS—Experience indicates that 90 per cent

is not well tolerated on the face and neck, and in almost every case 70 per cent should be used. 70 per cent in most other situations is as satisfactory as with 90 per cent. Where 90 per cent has proved too irritating, start with 50 per cent and then increase to 70 per cent as tolerance increases.

RECOMMENDED AREA OF APPLICATION FOR SPECIFIC DISORDERS

ACUTE BURSITIS—Start just below the ear on the involved side and carry over the shoulder halfway down the arm, and anteriorly to the mid-clavicular line and down to the nipple, and on the back to cover the scapula.

ACUTE TRAUMATIC DISORDERS—(Example: Ankle sprain)—Application to the entire foot and halfway up the leg.

ACUTE LOW BACK STRAINS—Start at the twelfth rib or just below the rib cage, in a band approximately 12 inches wide down to and including the coccyx, and laterally over both sacroilian areas.

ACUTE NECK STRAINS—The entire back of neck from the base of the skull down to and including the shoulders, and on the sides to cover sternocleidomastoid muscle.

OSTEOARTHRITIS OF THE KNEES—From six inches above to six inches below the patella all the way around the leg.

OSTEOARTHRITIS OF HANDS—Entire hand up to wrist with about 5 cc.

RHEUMATOID ARTHRITIS OF THE HANDS—Entire hand and halfway up the forearm or a similar wide area.

SCLERODERMA—Wide area application. The dose has been as high as 100 cc. and in a few instances almost total body application has been attempted. Therapy must be continued and the concentration increased to 90 per cent.

TIC DOULOUREUX OR TRIGEMINAL NEURALIGIA—If possible, apply to the entire side of the head and neck affected.

A. *Acute Inflammatory or Traumatic Situations.*
Some pain relief usually occurs within one hour. At 2 hours the pain is usually reduced by at least 50 per cent. Continue for three to seven days to assure that the condition does not recur.

B. *Chronic Conditions*
Response has usually been slower and the pain relief from a single or a few applications may be transient. A significant response may not be obtained until after 4 to 12 weeks of daily administration.

PRECAUTIONS AND CONTRAINDICATIONS

1. DMSO should not be used in infants, children or pregnant patients until adequate toxicity and teratogenic studies have been completed.

2. DMSO should not be applied to skin on which there is any drug or chemical.

3. As with any new drug, DMSO should be used with caution in patients with liver or kidney disease.

4. Some areas of the skin such as the face, neck, and axilla are more sensitive to the irritant properties of DMSO

than other areas. Also, individuals with blond or red hair seem to react more to the DMSO. The concentration should be reduced to 50 per cent or 70 per cent in these cases. (Note: Dilution of DMSO with water will produce heat. This is not a chemical reaction but only heat of dilution. There is no hazard involved.)

5. If any systemic allergic symptoms develop or there are any signs of general histamine reaction—generalized dermatitis, urticaria, wheal and erythema at sites distant from the original application, lingual edema, asthma, laryngeal edema—the DMSO should be stopped. The area should be washed with water to take off any excess. If appropriate to the clinical situation any other drug to counteract these symptoms (epinepherine, steroids, aminophylline) should be used.

ADVERSE REACTIONS

Approximately 85 per cent of patients experience a typical histamine-type reaction at the site of application, usually transient mild itching and burning and some erythema. This is not considered to be a true adverse reaction to the drug but a typical side effect. A fine vesiculation, occasionally at the site of application, is also usually transient. After prolonged administration, drying, mild wrinkling and occasionally some scaling of the skin is not uncommon. This is no worse than after a mild sunburn.

A few cases of generalized dermatitis have occurred. This is usually a wheal and erythema reaction of a histamine type occurring at sites distant from the area of application. Rarely may this generalized dermatitis be so severe. The drug should be discontinued if a generalized dermatitis develops.

Rarely, serious or potentially serious hypersensitivity reactions may occur. One fatal reaction has been reported in a patient who continued to receive the drug after signs of extreme sensitivity developed.

There has also been a report of laryngeal edema of a mild degree in one patient.

Other unusual reactions have included hypotension in a few patients.

A few cases of mild paresthesias have been noted. Re-evaluation of most of these cases has shown that these were in patients with a strong emotional overlay. Elimination of this type of patient from the clinical studies has greatly reduced this type of reaction.

Some patients have noted a tranquilizing or sedative effect. In most cases this has not been severe enough to warrant concern.

Sedation may occur more in elderly patients with cerebral arteriosclerosis. In the younger individual it occurs more often before meals. It may occur after the first application and, if it is observed, the patient should be cautioned about driving or pursuits that may harm himself or others. Some patients have noted an appparent potentiation of sedatives like barbiturates or alcohol. These findings have not been observed in the laboratory.

Some patients have a garlic or oyster odor on their breath after topical administration of DMSO. There have been a few cases of mild nausea. All of these effects have disappeared when the drug was discontinued.

ABSORPTION, EXCRETION AND METABOLISM OF DMSO— DMSO is absorbed through the skin and distributed through all tissues. The half life of DMSO in serum is about 48 hours. DMSO is excreted primarily in the urine, with some converted to dimethyl sulfide (DMS) which is excreted via the lungs.

Some of the DMSO is converted to dimethyl sulfone (DMSOO) which is excreted in urine over a period of days (1–15) after a single application. There is possibility of a gradual buildup of DMSO and dimethyl sulfone (DMSOO) in blood and tissue with repeated and prolonged administration.

CLINICAL TOXICOLOGY

Laboratory data are being accumulated on patients who have received DMSO by topical application to the skin for a period of one month up to 18 months. To date, there has been no evidence that DMSO produced kidney or liver damage or any significant or permanent changes in blood chemistries after topical application to the skin. No significant changes in the peripheral blood picture have been noted.

Blood chemistries have been followed on a large number of patients, and these have not shown significant changes.

If a patient is to be treated with DMSO for more than one week, pre-treatment laboratory studies should be obtained and repeated at four weeks and then at three months, and every three months thereafter as long as therapy is continued. No laboratory tests are usually necessary for acute conditions in which treatment is contemplated for less than two weeks.

Earlier studies included oral administration of the drug. This route of administration is not being investigated at the present time. (Oral and parenteral studies may be initiated at a later date.) These patients received 30 to 60 ml. per day orally for a period of two weeks, and weight loss from 5 to 10 pounds was noted in 50 per cent of the patients. This may have been from loss of appetite.

Although these changes in liver or renal function have only been observed following administration of large doses of DMSO orally, it is recommended that patients with liver or kidney disease be excluded from clinical trials with DMSO applied topically.

I was in Portland, Oregon, September 9, 1965, and I met Jacob and Rosenbaum at the latter's office. We were going to lunch at the nearby Roses's—a popular restaurant run by Ed's mother-in-law.

Both doctors looked tense, as we walked the hundred or so steps to the restaurant. Finally, Stanley mentioned it: "It had to happen sooner or later," he said sadly. "A patient died from medication—DMSO."

"All drugs are toxic," Rosenbaum said. "Why should DMSO be different from the rest?"

At this point, Jacob and Rosenbaum had only the sketchiest information. Someone on the telephone that morning said that someone else had read of the tragedy in the *Wall Street Journal*.

"It was a lady in Ireland," Jacob said. "As I get it, her tongue swelled and she choked. Apparently an allergic reaction to DMSO."

I was to hear for many years—and I am still hearing—about "the lady in Ireland" who died of a reaction to DMSO. Spokesmen for the FDA frequently allude to "the lady in Ireland" to justify their banning DMSO.

The story, written by William M. Carley, a staff reporter, appeared under the two-column headline:

DMSO MAY HAVE CAUSED DEATH OF WOMAN
MAKERS OF 'WONDER' DRUG WARN DOCTORS

In brief, an unidentified doctor serving an identified drug house (Squibb) had said the woman died after taking DMSO in an approved dosage along with penicillin (which regularly kills quite a few patients each year) and other drugs.

The story said in part:

New York—Drug companies began notifying doctors that DMSO, a so-called "wonder" drug used for pain relief, may have caused the death of a 44-year-old woman being treated with the medication.

The woman, who died three days after application of DMSO began, may have died of an allergic reaction to the substance, according to the warning notice.

The case gives the first indication that DMSO may produce dangerous side effects or allergic reactions.

Doctors cautioned that it hadn't been proved that DMSO caused the death. No autopsy was made. They also said that even if it were proved, the reaction might be so rare that it would still be worthwhile to use the drug in some cases.

Six drug companies are leading intensive investigation of the drug under FDA controls. The six are the Squibb division of Olin Mathieson Chemical Corp., Merck & Co., Syntex Corp., American Home Products Corp., Schering Corp. and Geigy Chemical Co.

Squibb supplied the DMSO used on the woman who died. A Squibb physician said she may have died of an allergic reaction, possibly to DMSO. In letters, the company warned about 100 doctors testing DMSO in the U.S. to halt use of the drug on a patient if allergic reactions showed up.

Merck also sent letters to doctors testing the drug. The company wrote it had learned of the death that was "possibly the result of treatment with DMSO" and also warned doctors to halt DMSO use if a patient showed allergic symptoms.

The Squibb physician gave this account of the death. The woman, who was living at her home in Ireland, sprained her wrist and knee. Her doctor instructed her to apply DMSO to the skin in those areas. On the first day of medication she developed swelling of the tongue and throat, shortness of breath and difficulty in breathing.

On the second day she applied the drug again and experienced the same reactions. Relatives suggested she call her physician but she decided to wait another day. Some time after visiting her doctor on the third day, she died. The Squibb physician estimated she had applied about 30 milliliters of DMSO, which is in the dosage range that the drug is being tested.

Doctors weren't sure that DMSO caused the allergic reaction and death, however, because other drugs were involved. The woman had previously developed a skin irritation from a hair-removing compound and the irritation developed into an infection. She received five injections of penicillin for the infection and this, plus iodine, cleared it up. The Squibb physician said there wasn't any apparent immediate reaction to the penicillin, but that there may have been a delayed reaction that caused death. Administration of penicillin began June 17 and application of DMSO began July 8.

The Squibb doctor also noted that the woman had been given a prescription for a drug to combat depression five days prior to the beginning of DMSO application. Whether the woman actually took the drug is unknown.

The Squibb report raises several questions: 1) Why the emphasis on DMSO when several other drugs (including some not mentioned in this account) were involved? 2) Why the *Wall Street Journal*? and 3) Was it because inexpensive DMSO was proving superior to many extremely expensive drugs?

A good deal of information was added later with publica-

tion of the first Annals of the New York Academy of Sciences 671-page report on the "Biological Actions of Dimethyl Sulfoxide."

Dr. Christopher H. Demos and three associates at the Squibb Institute for Medical Research, New Brunswick, N.J., reported the results of 76 clinical investigations involving the treatment of about 1,900 patients for a great variety of conditions, mainly in muscles and joints.

Perhaps the most noteworthy feature of the report was the fact that an extremely strong dosage was used—90 per cent DMSO and 10 per cent water liberally applied for up to five weeks. Patients very rarely are given DMSO in concentrations higher than 70 per cent, and even at that strength occasional transient rashes are noted. At 90 per cent concentration, 69 of the 1,068 patients with acute disorders quit treatment early, and 40 of the 848 chronic patients dropped out after only a few days or weeks because of local irritation. The major side effects were skin redness, roughness and itching. Other troubles, in the order of their frequency, were skin blistering, dermatitis and peeling. Thirty-three complained of the DMSO odor; 8 felt nauseous, and 11 showed swellings (edema).

The acute conditions, in the order of their frequency, were sprain, bursitis, strain, trauma (fractures and bruises etc.), myositis, tenosynovitis, neuritis, muscle spasm, arthritis, fibrositis, synovitis, tendinitis, etc. Chronic conditions ranged from arthritis, bursitis and myositis to neuritis sprains and less severe conditions.

In all, about 80 per cent of the acute patients showed improvement, and so did 60 per cent of the chronic group.

"We feel that DMSO is a unique and effective agent for the treatment of many acute musculoskeletal disorders," the Squibb group reported. "Beneficial results are unpredictable, but they occur frequently and are sometimes dramatic, particularly in acute conditions, which require low doses and

short treatment periods. In chronic conditions, improvement occurs at a lower rate and is less dramatic."

They also cautioned, "Local irritation is troublesome and causes a significant number of patients to discontinue treatment. The potential for severe allergic reactions, although rare, should be kept in mind."

These conclusions were based upon results with a superdosage (90 per cent DMSO) which few knowledgeable physicians would use today.

On September 22, 1965, Edward H. Nunn, the Crown Zellerbach general manager wired Jacob: "We received at 3 P.M. today a telegram from Mr. George P. Larrick, Commissioner of Food and Drugs, Washington, D.C., stating that our exemption for the clinical investigational drug use of dimethyl sulfoxide, IND 1310, has been terminated. The telegram states, 'Administration to human beings should be discontinued and the drug recalled from all clinical investigation.' Pursuant to this termination, we hereby direct that you immediately discontinue all further clinical investigation and return all unused portions of dimethyl sulfoxide to us."

Jacob and Rosenbaum could not regard the FDA's action as more than a bit of bureaucratic finagling—so absurd that it would be forgotten if ignored. Crown's new stern countenance they could have anticipated. For some time, the corporation and its principal officers had seemed jittery. Neither Jacob nor Rosenbaum felt any responsibility toward Crown.

Doomsday for DMSO, however, came about seven weeks later—on November 10, 1965.

Boost, calling from Syntex in Palo Alto, said: "Stanley, it's all over. The Food and Drug Administration has just halted research on dimethyl sulfoxide. They have sent out telegrams notifying the World Health Organization and the American embassies throughout the world."

The spirit drained out of the surgeon. This could mean the

end of DMSO, not only in the United States but everywhere.

When Rosenbaum picked up Jacob for a regular weekly drive to Salem, where they would treat Boost's mother, Jacob was still pale, and he seemed on the verge of tears. It was a dreary ride.

"What do you propose to do?" Rosenbaum asked on the return trip.

"Fight," Jacob said. "Naturally. We are doctors and scientists. We have an obligation to our patients and to humanity."

"The FDA can get tough," Rosenbaum reminded him. "And Crown can let us down."

"We'll meet those problems as they arise," Jacob said. His pallor had gone.

The FDA wasted no time in launching a barrage of publicity proclaiming the alleged blinding effects of DMSO. Within a few hours, the news media—domestic and foreign—had all the details, as served up by the FDA's alert corps of press agents.

Predictably, the editorial writers,inspired by the statements of the FDA spokesmen and the handouts, thanked heaven that the country once again had been saved from a thalidomide-type debacle. And the radio and TV commentators in their most solemn and sonorous tones did likewise.

In clinics throughout the land doctors reviewed their data to determine whether there was any suggestion of eye damage; they failed to find a single serious defect of any kind which reasonably could be laid to DMSO.

Jacob's patients called to ask, "Is it true that DMSO has made people blind?" He told them he knew of no such evidence. When they asked what they could do to continue DMSO treatments, Jacob told them they could write to their Congressmen.

The drug houses did not protest strenuously. In recalling unused DMSO from doctors, Syntex explained:

The changes observed in the refractive index of the lens in experimental animals—dogs, rabbits, and swine—do not appear to be related to the development of cataracts. In limited studies to date, this change has not been demonstrated in humans treated with dimethyl sulfoxide for prolonged periods of time at relatively high dosages.

In the affected animals, two zones appear in the lens, a central zone of variable diameter and a surrounding peripheral zone. The two zones are distinctly separate. It appears that this change represents a difference in the refractive index between the two zones, and both areas remain transparent. [Possibly indicating nearsightedness.] Microscopic examinations of sections of the affected eyes reveal no difference between the control and experimental animal.

The changes have been seen in dogs following oral administration of DMSO at all doses tested (1.0 to 40 ml/kg). Similar changes have been seen following topical (dermal) application of DMSO to dogs, rabbits and swine. The degree of these changes appears to be dose-related.

Crown Zellerbach first called Jacob demanding that he stop advising patients to protest. Then Crown followed with this telegraphic reminder:

This is to confirm our conversation and understanding on the telephone today to the effect that Crown Zellerbach Corporation is unalterably opposed to your advising any patients or others that they appeal to members of Congress or any other government officials, Food and Drug Administration and pharmaceutical companies' decision to suspend investigational use of DMSO. You agreed you would not further encourage any patients or others to pursue this course of action and will attempt to contact

those you have previously talked to to persuade them from this course of action.

True to his promise, Jacob contacted those he earlier had enlisted and asked them to call off their protests.

Meanwhile, volunteers were mobilizing spontaneously in rebellion against law and order as promulgated by the Food and Drug Administration. They included patients who felt the FDA had consigned them to pain, and disease and death; and they were led by doctors who had seen the healing effects of DMSO and who had decided the FDA was wrong.

This is the way Jacob and Rosenbaum later reconstructed events:

The two agents of the Food and Drug Administration—let us call them 006 and 009—were polite, businesslike. Jacob and the medical school administrators offered complete co-operation.

They began photocopying Jacob's files late in November 1965, and the continued busily through most of December. At times they would ask Jacob questions, and he would answer them. As time wore on, the agents became less friendly; their questions became more pointed; their comments were sharply critical of the record keeping.

Then one day, their picture taking took them to the animal care department—where they had no permission to explore. The director, Allan Rogers, protested to Joseph Adams, the Assistant Dean for Institutional Relations, who promptly summoned the two men to his office. One of them opened his camera and took out and destroyed the film. Mollified, the medical school officers then gave the FDA agents permission to go ahead and take pictures of the animal housing quarters.

The week before Christmas the agents asked to examine case records and a DMSO distribution file. Jacob gave them the go-ahead. Two days later, on December 21, 1965, Jacob said, he found the agents, with characteristic industry, photocopying his personal correspondence.

"Look," Jacob said to 006 and 009, "I know that this may be an honest mistake, but before you proceed further with the files I want your assurance that every photocopy so far made will be destroyed. Then let me know what you want, and I'll get it for you."

Jacob said 009 told him that since he had used government equipment and did the photocopying on government time, they couldn't give away government property.

Something shook Jacob's trust in these two men. The same agents had destroyed the government's film when they were caught taking pictures of the animal care facilities on government time.

"Are you kidding?" Jacob asked.

"No," 009 answered.

Bill Zimmerman, Assistant Dean for Business Affairs, called the FDA district director in Seattle and filed a protest on behalf of the medical school.

Rosenbaum entered his office one morning a half-hour late and somewhat tense. He had just rescued a patient in cardiac arrest, but he still wasn't sure the patient would make it. His waiting room was full.

Two surprise guests—009 and 012—were showing the receptionist their credentials. Because you don't keep important government representatives waiting, Rosenbaum took them into the consultation room, where they repeated the story told Jacob earlier.

Rosenbaum said the agents had a sense of humor. One of them said with disarming charm, "Look, we have no guns—no hidden microphones." And amid their laughter, both of them held up their arms, so anyone could see they were telling the truth. Rosenbaum gave them the records of about 200 of his 600 or 700 patients, sent them on their way, and went to work on his impatient patients.

The constitutionality of the FDA regulation which says that FDA agents may enter a physician's office and inspect

the records of patients on an experimental drug isn't above challenge. Even the insurance carriers' rights to invade patients' privacy may be a passing privilege.

Political figures, businessmen and beggars have secrets on the doctors' cards to which FDA plainclothes police were demanding access. An old venereal disease, marital troubles, a defective child or sibling, a chronic illness—these are among the confessions patients entrust to their physicians' files.

The FDA agents didn't bother to advise Rosenbaum of his rights: to remain silent, to have legal counsel.

Rosenbaum, worried, dialed Norman B. Kobin, attorney-at-law.

"You mean these agents demanded to see your patients' records? And you obliged them?" Kobin was incredulous.

"Yes," Rosenbaum faltered. "You see—"

"The agents violated your fundamental rights as a citizen," Kobin stormed. "And they breached a sacred doctor-patient relationship."

When the FDA inspectors returned a few days later for more records, Rosenbaum took them into an examining room. There he introduced them to Kobin's son, Chuck, also an attorney.

Chuck Kobin switched on a tape recorder. "Just so there won't be any misunderstanding," he explained. "Now, please explain your mission."

"For a half-hour, the agents hemmed and hawed," Rosenbaum said later. "When Mr. Kobin told them they were violating a patient-physician ethic by recording the names of patients, the agents said they would block out the names. Mr. Kobin advised them that he wanted, in writing, an explanation from their superior in Seattle."

Two days later one of the inspectors called from Seattle to complain that Rosenbaum was delaying the work of the FDA. Rosenbaum suggested the inspector talk to his attorney and pointed out that Crown Zellerbach and Merck had dupli-

cate records of his DMSO treatments. A few days later both inspectors again appeared in Rosenbaum's office and gave him a slip of paper threatening to invoke a federal regulation unless he surrendered the records.

"What regulation?" Rosenbaum asked. The inspectors said they didn't know.

That was the last Rosenbaum saw of them.

For several reasons, Stanley Jacob was reluctant to do what his common sense told him to do—hire a lawyer.

First of all, he couldn't believe his government wished him ill. Litigation meant time away from his work, a destructive distraction from his beloved DMSO.

And then there was the overpowering burden of expense. Only Jacob knew it, but he was desperately broke and going deeper into debt with each passing day.

Maybe if he didn't think about it, his trouble with the FDA would go away. The FDA would not go away, however.

And so Stanley Jacob asked Ed Rosenbaum to introduce him to Norm Kobin.

In the middle of the investigation, Ed Rosenbaum had a caller. "I work for the FDA," he said. "But I can't stomach what they're doing to you."

This is the way Rosenbaum relayed the agent's account to me:

> Two weeks after DMSO testing was stopped, almost every FDA inspector was called back to Washington for a briefing. It was the biggest call-back of inspectors that ever occurred. The inspectors were told that there was serious question as to whether the FDA had been right in stopping DMSO because of toxicity. They were told to go out in the field and find some "pigeons."
>
> The inspectors were interested in proving that the DMSO investigators had been dishonest. They were also

very interested in finding the names of any patients who had had side effects or bad results and who would testify to the damage before congressional committees.

The purpose was to try the original investigators int he press.

There was considerable jockeying within the agency for positions of power and for promotions. Everyone was jealous of Dr. Kelsey, who had received a medal for stopping thalidomide. And everyone was in hopes that they had another thalidomide or Krebiozen story to glorify the FDA and win promotions.

"He told me the smartest thing I could do was get myself a lawyer," Rosenbaum said.

Rosenbaum called Herschler and asked if Crown Zellerbach would provide a lawyer. Herschler seemed to think this would be in Crown's interest; but the next day Herschler called to say Crown refused. And neither would Crown associate itself in any way with Jacob and Rosenbaum, he added.

Rosenbaum had another visit from the friendly FDA agent. "He told me that FDA inspectors, in the guise of having me sign a permit to examine a chart, had me sign a blank sheet of paper," Rosenbaum told me.

He quoted his informant as saying, "The inspectors are down in the office now, laughing and wondering how to use your signature." He told Rosenbaum that the inspectors were copying Jacob's personal correspondence, and he gave Rosenbaum a copy of one personal letter of Jacob's which had nothing whatsoever to do with DMSO, Rosenbaum said.

At this point, Jacob and Rosenbaum decided they had better defend themselves.

Part Two

"I think I need help," Jacob said. "I should tell you, however, that I don't have a lot of money."

"More than money is involved here," the lawyer said. "We won't worry about it."

So Norman B. Kobin, attorney-at-law, took the case.

Kobin, a middle-aged, easygoing man, took the initiative. He wrote a letter to the FDA district director in Seattle protesting their agents' prying into Jacob's private and professional affairs on matters that had nothing to do with DMSO.

Kobin, as attorney for both Jacob and Rosenbaum, hoped to stop the harassment without triggering reprisals.

"The two FDA agents made an inspection and search of records belonging to Dr. Jacob far beyond the scope of the authority given," Kobin charged. "Unauthorized photocopies were made and taken from the premises." He demanded that the FDA return the photocopies forthwith and that "instructions be issued to the two agents and to all other agents of the FDA not to disclose any information gained as a result of this unauthorized search and seizure."

"This letter is directed to Seattle in order to afford your office the opportunity to correct this matter at the local level," Kobin conceded. "Should satisfactory compliance with this matter not be forthcoming within the next 10 days, we shall have no alternative but to take such steps on Dr. Jacob's behalf as may seem appropriate."

The answer to Kobin's challenge came from Washington, not Seattle. It was addressed to Jacob, not Kobin. It was signed by James Lee Goddard, M.D., the FDA Commissioner, who said he had been told that Jacob had expressed concern about the FDA's possession of the photocopies. Goddard wrote that it was his view that, with "very few exceptions," the copies of the documents were pertinent to the FDA investigation of DMSO; and he wanted to meet with Jacob to discuss which of the documents Jacob felt should not have been in the FDA's hands.

Kobin found little satisfaction with the FDA's response, particularly with the commissioner's argument that in effect, his police had honored Jacob's constitutional rights "with very few exceptions."

Ten days after he became Commissioner of the Food and Drug Administration, Goddard had received Kobin's note. Energetic, ambitious, deeply dedicated to law enforcement, a self-declared "activist," Goddard may have regarded the incident as heaven-sent. He was about to ask Congress for police powers which never before had been exercised in the United States over a category of citzens—scientists and physicians—for whom the law had been lax. The case of this Oregon scientist and the ridiculous panacea he was distributing far and wide may have seemed to offer perfect support for the FDA's position.

Goddard did not wait for Jacob to move. He presented the case against DMSO on March 9, 1966, at a hearing before the House of Representatives Fountain Subcommittee on Drug Safety, more formally called the Subcommittee on Intergovernmental Relations of the House Committee on Government Operations. Subcommittee people made no secret of their admiration for this keen-eyed, tense, lean civil servant; they liked his ready grasp of the agency's aims and the way he handled himself and his group of aides, whom he played as though they were chess pieces:

Mr. William W. "Billy" Goodrich, a lawyer with the title Assistant General Counsel, Department of Health, Education, and Welfare. Many considered him the architect of the latter day FDA;

Dr. Frances O. Kelsey, his Chief of the Investigational Drug Branch, who had been given a gold medal by President Kennedy for supposedly keeping thalidomide out of the United States;

Dr. Joseph F. Sadusk, Jr., Medical Director, whom some had considered heir apparent to the commissionership until Goddard came along; and

Dr. Robert M. Hodges and Dr. Harold Anderson, a couple of bureau wheelhorses.

Goddard opened and introduced himself to the subcommittee with a background sheet and an FDA press release on President Johnson's announcement of his appointment. The data included: born, April 24, 1923, in Alliance, Ohio; married, three children; *EDUCATION:* Warren, Ohio, high school; Mount Union College, Washington and Lee University, Temple University, and, for his M.D. in 1949, George Washington University School of Medicine. He was in the Army 1943–46. As an officer of the U.S. Public Health Service during and after his internship and with other government bureaus in 1949 until he became FDA Commissioner on January 17, 1966, he had served traineeships in the New York State Department of Health in Albany, the Harvard School of Public Health and the District Health Department in Chapel Hill, N.C.. He was a member of a dozen medical groups; and under *"Awards"* he had listed three earned in 1962: the John Jeffries, the P.H.S. Meritorious Service Medal and the Distinguished Service Award of the Federal Aviation Agency.

In the seventeen years since he had won his M.D., Goddard had been in private practice a total of fourteen months.

With this background, he was now to wield unprecedented, some charged almost dictatorial, power over the practice of medicine in the United States.

Goddard himself outlined to the Fountain Subcommittee the requirements, under the 1962 Kefauver-Harris Amendments to the Pure Food and Drug Act: in Phases One and Two of testing, drug houses must present complete data on a proposed drug—chemical, biological, source, strength, purity. They must identify those who will test the preparation in the laboratory, give their qualifications, and list the facilities. With animal data compiled, Phase Three—final clinical trials—may be undertaken; this calls for detailed physical and chemical examination of subjects given the drug, careful recording of data, and periodic reports. Sponsors could not advertise or sell the drug while under study.

Goddard said the FDA retained the right to order an investigation discontinued if there were false or incomplete data, deviation from the plan, signs of ill effects, lack of effectiveness, inadequacy of facilities or controls, elements of commercialization, or indication that the plan was unreasonable.

"I fail to see how anyone could disagree with the purpose of the regulations," Goddard said.

The committee members nodded agreement with the bright, earnest new commissioner.

Goddard's testimony before the Fountain Subcommittee on March 9, 1966, was a product not only of his own long experience in bureaucracy but also of the genius of Billy Goodrich, the FDA's playmaker, author of many of the statements read, and the commissioner's coach throughout the session.

Goddard testified: "I am instructing the formulation of clear internal policy and procedure guidelines for the performance of adequate surveillance over the conduct of clinical investigations under IND's. We believe such attention will improve the quality of performance and the probative value

of research. *We have a delicate problem in investigating the investigator.* [Emphasis mine.] Scientific personnel are not accustomed to being questioned by regulatory agencies. But some investigations will have to be made and when it becomes necessary to do so every effort will be made to minimize misunderstanding."

To minimize any of the subcommittee's misunderstanding of the need to lend his bureau a few of the citizen's liberties, he outlined briefly the FDA's charges against Crown, Jacob and DMSO.

Goddard said:

> In October 1963, a plan for the clinical investigation was filed. Review showed the animal studies to be so incomplete as to warrant only the most limited of use in human beings, and the firm was advised that approval extended only to external application of the skin of DMSO alone, not combined with any substance other than water, and limited as to factors of duration and concentration.
>
> The firm made arrangements to license the use of DMSO under their patents to six large drug firms, each of which in turn filed the required plan of investigation. We have found that in the next 2 years, one or more of the firm's investigators:
>
> (1) Disseminated glowing reports of the speculated value of the drug in a wide variety of conditions.
>
> (2) Had performed some further animal studies which, when submitted, were believed by them to warrant gross expansion of the clinical studies although no such expansion was justified by the studies.
>
> (3) Distributed the drug to many physicians who wanted it simply for the purposes of therapy, without exercising any of the safeguards necessary to clinical investigation, and without many of these physicians being listed as investigators.

(4) Exported substantial quantities of the drug without regard to the requirement of the law or the reporting requirement of the investigational plan.

(5) Failed to report new investigators and new procedures of use beyond topical application until long after the studies were underway.

(6) Never initiated the comprehensive animal studies which had been originally requested by FDA as a basis for Phase Three investigation.

(7) Encouraged use of the drug by oral administration, injection, bladder irrigation, application to mucous membranes, application to the eyes, use for conditions not specified in the plan, and use in combination with a wide variety of other drugs, for which conditions there had been no suitable safety data supplied.

Speculation and enthusiastic promotion both to the profession and to the public was substituted for scientific inquiry and deliberate evaluation of evidence. This resulted in unwarranted distribution for use as a therapeutic agent by many physicians, before the animal or human studies had established either safety or efficacy.

Plainly, the plans submitted to use did not cover what was actually being done, nor did the data available to use or to the sponsors provide an adequate basis for the broad-ranging distribution of this investigational new drug.

Goddard mentioned that the FDA had warned one of the drug companies in June 1965 about illegal use of DMSO. He told of the refractive changes in the lens of the eyes of some test animals and the suspension of all investigational use of DMSO on November 11, 1965.

"I have, however, permitted continued use for a few investigators to administer to specific patients—about 50—having the conditions scleroderma, tic douloureux, Raynaud's phenomena, and multiple sclerosis," Goddard said.

Goddard served notice that "we are investigating possible criminal violations." This remark was headlined throughout the United States.

It fell to Sadusk to justify the FDA's program.

Sadusk could be—and was—fairly specific about the toxicity detected in animal studies: the changes in the refractive index in dogs fed DMSO and in rabbits painted with DMSO. He neglected to point out, however, that 100 times the human dose had been given the animals.

It is noteworthy that Sadusk at one point could complain that "very extensive publicity appeared in the popular press, representing DMSO to be a wonder drug for the treatment of a variety of diseases" and a few minutes later tell of the FDA's resort to the press release to warn "of the dangers of DMSO" to the human eye, another charge without any proof.

Sadusk cited—but did not identify—reports suggesting a "probable relationship" of DMSO to "impaired vision of a vague type," "decreasing vision," "pain in one eye," etc.

He said that systemic allergic reactions had been reported "with at least one death." Yes, the lady in Ireland.

Sadusk submitted a catalogue of "Adverse Reactions to DMSO" which he said had been reported; but he neglected to say by whom, or where, or when, or how. And nobody asked. The complaints included:

SKIN—damage to the mucuous membrane of the mouth and sloughing at the treated area (four cases);

BLOOD—monocytosis and leukopenia (four cases);

CARDIOVASCULAR—congestive heart failure (one case) and tachycardia, or pounding of the heart (two cases);

LUNG—pneumonitis (two cases), shortness of breath (two cases);

LIVER—hepatitis, "although there does not appear to be a cause-effect relationship" (three cases);

CENTRAL NERVOUS SYSTEM—headache, vertigo, drowsiness (fifteen cases), severe mental confusion (one case);

GASTROINTESTINAL—mostly mild, nausea with or without vomiting (apparently related to garlic taste or odor) (thirty-four cases); and transient GI bleeding (one instance).

"There have been a small number of reports evaluated as not cause related, of cerebrovascular accidents, myocardial infarction, depression, mental confusion, possible abnormal liver function, panmyocarditis, and gastrointestinal bleeding occurring in patients using DMSO," Sadusk testified.

Present at the Fountain Subcommittee session the next day were FDA administrators, doctors and press agents, and six representatives of four drug houses (Wyeth, Squibb, Geigy and Merck Sharp & Dohme).

But there wasn't anybody there to defend Stanley Jacob or ask for proof that DMSO was harming and killing people.

Of the more than 70,000 patients enumerated by the FDA at the hearing as having been treated with DMSO on IND's issued to fifteen sponsors other than Crown Zellerbach (Maxwell Abramson, M.D.; Ayerst; Geigy; Robert E. Gosselin, M.D.; Eli Lilly; Merck; Chas. Pfizer; Procter & Gamble; Sandoz; Schering Corp.; Arnold Seligman, M.D.; Squibb; Syntex; White Labs; and Wyeth Labs), not a single one had been invited to testify as to whether DMSO did him good or ill.

After reading newspaper accounts of the hearing, Jacob fired off this telegram to Fountain:

> If the newspaper reports of Dr. Goddard's testimony before your committee are correct, he has done a disservice to himself, his agency and the American people. According to all scientific evidence available, Dr. Goddard's statements of eye damage in man are simply and absolutely not true.

Neither Fountain nor his committee acknowledged the telegram.

Shortly after the Fountain Subcommittee hearings, Sadusk

quit the FDA. He worked briefly as Professor of Medicine at Johns Hopkins before following the custom of many former FDA officials—taking a job with the food or drug industry. Sadusk became Vice President for Medical Affairs with Parke, Davis and Company in Detroit.

A few weeks after retiring—on May 17, 1966—he submitted an article, "Drugs and the Public Safety," to the *Annals of Internal Medicine* which was particularly eloquent in what it didn't say. It didn't mention Goddard, for example, although it did praise the "highly dedicated public servants, both medical and nonmedical, both scientific and regulatory," with whom he had worked. Perhaps more pointedly, he paid tribute to "the skillful leadership and guidance which Commissioner Emeritus George Larrick gave to the Administration."

To warn the medical profession of imminent danger—and, one might speculate, possibly in contrition for his own role in the FDA—he wrote:

> No one can deny that the provisions of the Federal Food, Drug and Cosmetic Act and its amendments are in the public interest and promote drug safety to a degree not surpassed anywhere in the world. But it must be recognized—and this I cannot stress too strongly—that the provisions of these drastic and far-reaching amendments should be administered in a scientific and flexible manner. An overly strict interpretation and application of the legal and regulatory language of the recent amendments could stifle the development and production of new drugs.
>
> The Food and Drug Administration must arrive at decisions on the basis of a consensus of informal medical opinion, both within and outside the Agency. And above all, the government has an obligation under the law to fully inform the practicing physician on the efficacy and safety of drugs but not to go beyond this point. To tie the hands of the doctor by dogmatic directives in the labeling on the use

of a drug, to overemphasize adverse animal data without clinical confirmation, or to stress adverse experiences without a reasonable degree of certainty of a cause-effect relationship is unjustifiable. I hope that all practicing physicians will demand for their patients the privilege and right to prescribe that drug which in their opinion is the best drug to be used at the time of treatment and under the circumstances which surround that treatment. It must be the physician, as the patient's doctor, who maintains the ultimate responsibility for the treatment of his patient.

In the same article, Sadusk berated the press for having quoted some scientists' fears that "the pill" to prevent pregnancy was not proved safe, that, for one thing, it might cause thrombophlebitis.

"This is a matter on which there has been much loose talk and speculation, and for which highly sophisticated procedures will be required to completely clarify the matter," he wrote. He said that with 5,000,000 American women taking the pill, it was surprising that many thousands more cases of thrombophlebitis had not been reported due to natural causes. "It is sad to note that many women using these drugs have been unnecessarily alarmed by biased and misleading articles appearing in the lay press and prepared by certain self-appointed experts. It should be the duty of the press to stress conservatism and scientific accuracy in reporting, particularly on matters of drug safety."

While Sadusk's statement was designed to quiet fears, it also tended to promote the sales of the pill. Inadvertently, of course. The Merck Manual of 1966, a standard medical reference, and later, the *AMA Drug Evaluations—1971* warned of an enhanced risk of thromboembolic disease associated with the pill in British and American studies. The pill was found also to increase the chance of hypertension and anemia, as well as clots, in women and monster offspring in mice. Sadusk wrote his paper well before he joined Parke,

Davis, which happens to produce a contraceptive called Norlestrin, and, as he might put it, his paper and his new job probably are not "cause-effect related."

Many months after he had entered industry, I wrote to Sadusk and asked how he then felt about DMSO's toxicity. He said he had had no further contact with the drug since leaving Washington, and he added, "It may be by now that the FDA has sufficient early experimental data to arrive at a new stand."

The FDA, however, was doing business at the same old stand. In January 1968, with a growing disaster having overtaken the nation's introduction of new drugs, the FDA relaxed its rules somewhat, for all drugs but two—LSD and DMSO.

The Fountain Subcommittee session served to establish Goddard as a tough commissioner and the threat of investigation as a powerful bureaucratic weapon to keep the profession, the drug industry and the public in line.

A month after Goddard had tested his authority and found it functional before the Fountain Subcommittee, he distributed a note to "Dear Mr. Chemical Supplier," "to ask your help" in the problem of hallucinogenic drugs. He warned, in closing: "Failure to take action to determine legitimate use of these chemicals may result in unnecessary investigations of your activities and possible regulatory action."

Ten days later, Goddard admonished doctors in a luncheon address at the annual meeting of the American Society of Internal Medicine to practice better medicine and assume their responsibilities. "The Food and Drug Administration is a third party in the practice of medicine," he said. He urged his audience to consider the FDA's "recent experience with DMSO."

He was even more hard-boiled with the drug industry and with those who wrote the advertising. He charged industry executives with "excess in advertising," "misleading statements," "an overabundance of information available to

the physician," in the industry's free books, periodicals, direct mail letters and other means of reaching the doctors. Some editorial writers charged that Goddard was following the familiar course toward imposing censorship.

And more and more commentators asserted that the role of the FDA, "the third party in medicine," had become that of Big Brother.

Goddard continued to pay his visits to congressional committees, each time with new success . . . and more power.

The generous gift of police powers awarded to Goddard was not inspired solely by the thalidomide horror, or the abuses of DMSO. The most impelling force, from the public's point of view at least, was the drive against so-called "dangerous drugs," the ghastly stuff that was turning an entire generation of youngsters into killers, arsonists, lunatics, thieves, whores, pimps, gunmen and the walking dead, to satisfy a habit that very few ever could or would shake.

Goddard delineated for the Fountain Subcommittee the authority granted him under the February 1, 1960, Amendments to the Narcotic and Drug Abuse Act. In a statement covering twenty-one pages of single-spaced type, the commissioner said that "the law, as it currently exists, is a good law and one which we feel will enable us to deal with the problems."

He said the amendments:

1. Provide for control over the manufacture of depressant or stimulant drugs and *any drug which contains a substance found by the Secretary of Health, Education, and Welfare to have a potential for abuse because of its depressant or stimulant effect or because of its hallucinogenic effect;*

2. Eliminate the necessity for the Government to prove interstate shipment of them;

3. Require wholesalers and jobbers of the drugs to register with the FDA annually and manufacturers to indicate if they are producing them;

4. Provide that inspectors may:
   a. execute seizures with or without libels of information,
   b. execute and serve arrests and search warrants,
   c. make arrests without warrants in certain cases, and
   d. carry firearms.

"The backbone of our field staff will be composed of criminal investigators," Goddard reported. He said 175 of them—almost all former federal enforcement agents—already had been hired, some as gun toters.

It became evident within the first few months after the FDA had been armed with unprecedented police powers that the agency had scored instant and almost complete success against one "dangerous drug"—DMSO. Most physicians returned their stores of DMSO to the supplier or destroyed them. To have DMSO on the premises was to court raids by FDA agents and criminal prosecution. To continue to use it in the clinic was to invite malpractice suites as well; complainants could cite the FDA attitude to indicate that the physician was in the wrong.

Dr. Marvin Paul of Toronto had written that a big meeting on DMSO should be held in the United States, and Bob Herschler had sounded out the New York Academy of Sciences.

The academy had responded promptly and positively. It had received similar suggestions from two other independent sources; if a program were prepared the academy would like to consider it.

Everything went well until September 1965, when the FDA suddenly cracked down, charging that the number of doctors testing DMSO for Crown and the number of patients were far greater than the maximum the FDA had permitted.

DMSO, not merely as a new drug but representing a whole new principle in medicine, had attracted physicians and patients in enormous numbers.

Crown's reaction was complete and abject compliance with the FDA's orders. His bosses ordered Herschler to renounce his role with Rosenbaum and Jacob, and this Herschler did. At his age with only a bachelor's degree, new jobs were not easy to find.

The New York Academy is big (almost 27,000 members in fifty states and many foreign countries) and broad (it sponsors meetings for a vast array of scientific disciplines). Its leaders have forged outstanding reputations in their own fields—and many have taken their lickings for creativity. In

this organization, stuffy inner politics and do-nothing bureacracy are at a minimum.

Jacob had spent the summer of 1965 writing letters to everyone he knew who had studied DMSO, regardless of whether they thought well or poorly of the compound, and by September he had collected about 100 abstracts on which to propose a program.

Two weeks after Crown Zellerbach was ordered to cease sponsorship of their IND, Dean Baird called Jacob into his office and told him that Crown was bringing great pressure on him to have the New York Academy symposium called off.

"I can't order you to withdraw from leadership in the symposium," Baird told the young surgeon. "I don't regard that as the kind of authority a dean should exercise in a decent and democratic educational institution. My concept of academic freedom, however, does not forbid my advising you that if you go ahead with your present plans, you might embarrass the dean."

Jacob studied his friend. "Under no circumstances would I embarrass the dean," he said, and he repeated: "Under no circumstances."

The dean smiled and said, "But since Dr. Rosenbaum isn't a member of the faculty at this time, I have no control over him. If he were to go ahead and develop the symposium—"

So Ed Rosenbaum went to Two East Sixty-third Street, New York, to negotiate for the proposed meeting. He was amazed at the grasp the academy officers had of the situation and of DMSO. He said that with the large number of papers to be presented, the meeting should run three days, and he would like to hold it seven or eight months hence, in the spring.

The academy officers pointed out that meetings of this size were held usually at the Waldorf Astoria Hotel, which was booked solidly through the spring, and, anyway, other arrangements would take more than one year.

No sooner had Rosenbaum gotten back to Portland than the Academy called Herschler to tell him that, on second thought, the DMSO meeting was so important that a special case was being made for it. If a program could be produced in thirty days, they'd schedule the meeting for March 1966, five months off.

"I wondered about this, and I still do," Rosenbaum said years later. "My guess is that the FDA tried to 'persuade' the New York Academy to call off the meeting. The officers were not men who can be intimidated."

Dean Baird and Jacob (Herschler now was dropping farther and farther into the background) induced Dr. Chauncey Leake of the University of California Medical Center, one of the most respected and powerful figures in medical education, to agree to chair the symposium.

Jacob bent his efforts to seeking negative papers to give the program some balance. It turned out that it was virtually impossible to find knowledgeable scientists who could offer negative or unfavorable reports. He invited Sadusk to send FDA researchers to report; the FDA official replied he would be delighted to oblige, "but rumor has it that the symposium never will be held." His reply came on November 9, 1965—the day before he issued the order banning DMSO research.

When Rosenbaum met Leake in New York he apologized. "We'll understand perfectly if you elect to withdraw now," Rosenbaum said.

"Not a chance, Ed," Leake said. "Let's get to work on the details." They were to present their plan and program to the academy's executive committee for its approval that evening.

Leake asked whether any drug house might pick up the tab for expenses, which, for a meeting of this sort, usually ranged form $20,000 to $50,000.

Rosenbaum's jaw fell. He hadn't thought of this. And with Crown Zellerbach possibly wishing it had never heard of DMSO, there wasn't a chance of support there. The drug

houses, too, had lost interest. Both men, deeply discouraged, reported that they would have to call the meeting off after all. The academy told them, "that won't be necessary. The academy has special funds for this meeting. Don't worry about money."

Leake then received a call from a drug industry leader whom he chooses not to identify. After the conversation, Leake told Rosenbaum, "My friend asked that we drop plans for the symposium at this time—said it would be very embarrassing to both the drug houses and to the FDA." He decided to call Dean Baird.

After hanging up, Leake turned to Rosenbaum. "Know what Baird said? He said, 'Chauncey, when have you or I, as deans and educators, ever let political or economic considerations compromise the search for scientific truth?'"

Leake didn't talk about it then. As they got up from the dinner table, he said, "Okay, Ed. Let's give the committee our program."

When Leake announced their decision, the committee applauded. "They seemed to have a special interest in this," Rosenbaum said. "It was as though a tenet of scientific morality had been tried—and triumphed."

The March 14, 15 and 16, 1966, symposium under the auspices of the New York Academy of Sciences was held in a large hall of New York's Waldorf Astoria Hotel. More than a thousand researchers came from all parts of the United States and from overseas. After the FDA had cracked down on DMSO, Jacob had written to every person who had submitted an abstract; he said that now that DMSO had been branded toxic and dangerous by the FDA the paper could be withdrawn. No one canceled.

In opening, Dr. Leake jocularly welcomed agents of the Food and Drug Administration and Federal Bureau of Investigation, who were conspicuous by their apathy.

Eighty-two papers had been scheduled, and many addi-

tional scientists spoke extemporaneously. With perhaps one exception, Dr. Arthur Ruskin of the FDA, who concentrated on the fine job being done by the FDA and its tolerance of science, the papers reflected virtually unanimous enthusiasm for DMSO's unusual physical, chemical and medical properties. Ruskin's message was, "this symposium is a measure of the freedom of investigation and the responsibilities for it of the United States Government prevailing in this country."

One section was concerned with DMSO's phenomenal ability to protect living cells and organisms against the damaging and lethal effects of cold and of radiation. Both properties held implications for cancer—DMSO might shield normal tissues in cryosurgery or in supervoltage radiation. Dr. M. J. Ashwood-Smith of Harwell, England, one of the earliest experimenters with DMSO, said he thought the two protective mechanisms might be related.

Papers on DMSO toxicology and pharmacology and others dealing with DMSO's effects on plants and microscopic organisms, told of labeling DMSO with radioactive atoms so that the compound could be traced during its anatomical travels, chemical changes, membrane penetrations, and effects on enzyme systems in nerve cells (giving at least a hypothetical mechanism for its tranquilizing and pain-suppressing effects). Others reported on its influence on coagulation, on antibody, lysosomal and other immune systems, on hormones like cortisone, on a number of skin diseases.

Many speakers confirmed Jacob's early observations in animals and in man. The studies covered a spectrum of diseases probably far greater than any ever before considered in relation to a single drug.

As the New York Academy sessions were drawing to a close, an FDA agent turned to Ann Sullivan of the Portland *Oregonian*, and said, "DMSO is through."

Ann looked at the man in amazement.

"Where did you ever get that idea?" Miss Sullivan asked.

"My boss told me," the agent answered, according to Miss Sullivan.

The papers presented at the academy sessions were published in a brown paperback volume of 671 pages and several hundred thousand words, *Annals of the New York Academy of Sciences*, Volume 141, Art. 1, *Biological Actions of Dimethyl Sulfoxide*. If it isn't out of print, it can be bought for about fifteen dollars.

Here in a nutshell are some of the points made at the academy meetings:

TOXICITY—Several investigators reported that very high doses of DMSO, often administered by unusual routes, produced clouding of the lens in three animal species. These effects could not be repeated in humans or related species, and some reported they were reversible to a degree.

FREEZING—DMSO overcame the effects in several species.

RADIATION—DMSO strongly protected against lethal x-rays—much moreso than did AET, cysteamine and serotonin (Ashwood-Smith). Moreover, DMSO was effective even when applied only to the skin (F. Golan, Univ. of Miami).

TOXICITY—LD-50 values (the dose needed to kill 50 per cent of the test animals) show DMSO has low systemic toxicity (by oral, intravenous, topical, subcutaneous and intraperitoneal routes) to nine subhuman species. Eye changes appear to be irreversible (Emil R. Smith et al., Mason Research Institute, Worcester, Mass.).

TERATOGENICITY—Injected into chicken eggs in very high

doses, DMSO caused birth defects. Pregnant rats, mice and rabbits injected in the belly with high and repeated doses of DMSO occasionally produced defective offspring (F. M. E. Caujolle et al., Toulouse, France). Hamsters were even more susceptible (V. H. Ferm).

PLANTS—DMSO enhanced the phosphorous uptake—and presumably metabolism and growth—of strawberry plants and young pear trees (Ralph Garren, Jr., Oregon State Univ.). DMSO transported bactericides and fungicides into plants and cured or controlled serious infections of peach, plum, apricot, nectarine and other trees (Harry L. Keil, U.S. Dept. of Agriculture, Beltsville, Md.). DMSO transported iron nutrients into citrus trees (C. D. Leonard, Univ. of Florida).

HORMONES—DMSO increased the potency of cortisone-type hormones in cultured cells (D. Berliner, Univ. of Utah).

CANCER AND LEUKEMIA—Organisms frequently found in cancer and leukemia patients and suspected as a cause of cancer stopped growing when exposed to 25 per cent DMSO (F. Seibert et al., Mound Park Hospital Foundation, St. Petersburg). DMSO killed leukemic cells more readily than normal cells growing in the same culture (Robert Schrek et al., V. A. Hospital, Hines, Ill.). DMSO neither speeded nor slowed the growth of cancer cells implanted in the rabbit belly (James R. Armstrong, La. State Univ.).

HEART DISEASE—DMSO plus hydrogen peroxide released oxygen to the heart muscle of small laboratory animals inflicted with a coronary artery closure. The combination seemed to protect the hearts from some damage (J. Finney et al., Baylor Univ. Med. Center, Dallas).

NERVE CONDUCTION—6 per cent DMSO slowed conduction of impulses along the isolated frog leg nerve (W. Mitchell Sams, Jr., Letterman General Hospital, San Francisco). DMSO exerted a reserpine-like tranquilizing effect, but it also lowered the convulsant threshold in animals—the effect could be overcome by the anti-convulsant alphagluco-

chloralose (AGC) (Monique C. Braude, Univ. of Md.).

TOXICITY—DMSO dosages ranging from weak to strong were injected into the veins of lightly anesthetized dogs with "remarkably few alterations" in heart-lung function, nerve reflexes and basic blood chemistry (Clare G. Peterson and Ralph D. Robertson, Univ. of Ore. Med. School).

ALLERGY—DMSO either prevented or greatly enhanced a type of allergic reaction known as the Schwartzman phenomenon. In this, an allergen is injected into the skin of the leg of a rabbit; when the same allergen later is injected into the vein there is a dramatic eruption at the previously prepared site on the leg. DMSO affects this, depending on how and when DMSO is administered. If 90 per cent DMSO is applied over the site where and when the allergen (a bacterial toxin) is injected into the skin, a later intravenous injection of the allergen results in a big and bloody reaction at the site of the first injection. If, however, the 90 per cent DMSO is applied to the skin at the time of the second toxin injection, it prevents the reaction completely. If a very small amount of 70 per cent DMSO is injected intravenously along with the toxin, death ensues within hours. While 70 per cent DMSO probably never would be injected intravenously, these experiments indicate that DMSO, concentrated, can be a two-edged weapon, capable of great good and possibly great harm in allergy (James R. Ward, Morgan L. Miller and Stanley Marcus, Univ. of Utah).

ENZYMES—DMSO dissolved every enzyme studied without irreversibly altering it. Inasmuch as enzymes often represent the chemical expression of specific genes, DMSO may help compensate for bad genes (D. H. Rammler, Syntex Research Institute, Palo Alto, Calif.). DMSO increases the activity of some enzymes (Carl Monder, Hospital for Joint Diseases, New York).

BLEEDING—DMSO, in different concentrations, seemed to control the mirror image dangers of bleeding and clotting. At under 1 per cent, DMSO speeds clotting; at 5 per cent or

higher, it slows or prevents clotting (Herbert L. Davis et al., Univ. of Neb. College of Med.).

CELL SANITATION—DMSO has increased from ten- to a thousand-fold the ability of cortisone and other chemicals to stabilize lysosomes, bags of the cells' scavenger enzymes (Gerald Weissmann et al., New York Univ.).

EYE DAMAGE—Dogs force-fed fifty times the human dose of DMSO five days a week for nine weeks developed changes in the lenses of their eyes. The changes cleared up, but not completely, when the DMSO was withdrawn. The same thing happened in rabbits and swine once or twice daily swabbed with high doses of DMSO for three months (Lionel F. Rubin, Univ. of Pa., and K. C. Barnett, Univ. of Cambridge). Rabbits fed about a hundred times the average human dose of DMSO for from seven to ten days developed lens changes which appear to be due to the loss of soluble proteins of the lens. The same dose applied to the rabbit skin was virtually without effect (Don C. Wood et al., Providence Hospital, Portland).

Dogs force-fed large quantities of DMSO for fourteen weeks and longer, developed a strange "lens with a double focus," much different than the change in refractive index caused by insulin, the sulfas, Diamox, aspirin-type compounds, ACTH and the miotics or as an aftermath to flu, rheumatism, tetany, jaundice, encephalitis, nephritis and TB (Kurt Eberhard Kleberger, Free Univ., Berlin).

A total of 108 patients with complains involving 157 eyes were given 7.5–66 per cent DMSO topically for up to more than one year. Only one developed a lens opacity, which did not increase during nine additional months of DMSO therapy and was laid to causes other than therapy. The DMSO benefited patients with corneal edema and some, but not all, with eye inflammations (Dan M. Gordon, Cornell Med. School).

Thirty patients in Germany were treated for as long as eight weeks with DMSO in one series (and two hundred eighty others for various periods) without detectable ill ef-

fects to the eyes. "I think it should be mentioned that the topical dosages required to produce these (eye) changes in animals are astronomical in relation to the human dosage" (Gerhard Laudahn, Free Univ., Berlin, and Schering AG).

EPISIOTOMY PAIN—Topical application of DMSO for a few days following the severing of perineal tissues (to permit unimpeded birth and prevent the tears which sometimes result) reduced pain and edema but not enough to make the use of DMSO in this situation worthwhile (Irvin C. Arno et al., Albert Einstein Med. Center, Philadelphia).

CARCINOMA IN SITU—Barium-containing intra-uterine contraceptive devices often transform cervical smear cells into localized cancer or pre-malignant cells. DMSO with decadron alters the smears toward normal (J. Ernest Ayre and J. LeGuerrier, National Cytology Center, New York and Miami).

HORMONES—When DMSO was added, it increased the penetration of cortisol and testosterone through the skin 350 per cent (Howard I. Maibach, Univ. of Calif. Med. Center, San Francisco).

EAR, NOSE, THROAT—DMSO, alone and in combination with antibiotics (like tetracycline and erythromycin), wrought good to excellent results in such conditions as acute otitis media (but not chronic otitis media), nose or ear furuncles or inflamed pockets of pus, impetiginous eczema, tonsilitis and pharyngitis, aphthous stomatitis and malignant thyroid in the neuralgic type of head pain. DMSO widely applied to the forehead, neck and whole face sometimes provided sensational relief. Also benefited were temporomandibular neuralgia, hematoma (in which blood collects in a series of vestibules under the skin), cold sores and shingles (Hans Asen, Berlin).

ALCOHOL—In laboratory animals, DMSO, given beforehand, reduced deaths from lethal doses of alcohol; but DMSO increased the mortality when given after alcohol had taken effect. A pony of cognac will reduce the smell of

DMSO (H. J. Mallach, Univ. of Tubingen, West Germany).

VETERINARY—DMSO often helps repair trauma effects in horses (M. D. Teigland, Florida Atlantic Univ.).

DMSO was of benefit in small animals with mammary engorgement, mastitis, post-surgical stasis, interdigital cysts and skin scurfing (Robert P. Knowles, Univ of Miami).

It reduced considerably mortality from panleukopenia, a highly contagious blood disease of cats (Charles D. Dake of Ontario, Oregon).

When DMSO was painted on the open wounds of horses, it stimulated "fantastic" healthy granulation during the first few days; bacteriostatic properties were shown after a few days when badly contaminated wounds cleared up without pus formation, and a protective film formed over the wound surface. DMSO reduced excessive granulation to normal in one month (Francois Levesque, School of Veterinary Med., St. Hyacinthe, Canada).

POST-SURGICAL PAIN—Following open chest surgery for lung cancer, aortic aneurism, pulmonary tuberculosis, emphysema and hiatal hernia, the 12–15-inch thoractomy incision was painted with 60–80 patient DMSO every six hours. As compared with control patients, who received 10 per cent DMSO, the experimental subjects required only one half the usual amount of morphine and analgesics; and they coughed more easily, moved about better in and out of bed, had fewer complications (like ileus, nausea, vomiting and constipation). DMSO-treated patients did not develop pneumonia; and their post-operative course was less complicated and more rapid than that of the controls. Most subjects noted a moderate burning sensation during the first two or three applications; there was the odor, dryness and peeling; and DMSO was withdrawn from one patient who developed a localized rash (Dale S. Penrod et al., Pennsylvania Hospital, Philadelphia).

ACUTE MUSCULOSKELETAL CONDITIONS—A total of 187 patients with bursitis, tendinitis, sprains and strains in an un-

controlled series and ninety-two comparable others in a double-blind controlled series were treated with 60–90 per cent DMSO or, as a placebo, 10 per cent DMSO. A mathematical system of grading pain, tenderness, edema, limitation of motion, effectiveness and side effects was devised; and note was made of each patient's age, hair color, ethnic background, geographic origin and other variables. About 85 per cent of the DMSO-treated won excellent and good scores as compared with none of the placebo-treated; the pain scores for the DMSO-treated dropped from an initial 2.85 to 1.26 at one half hour, 0.45 at one hour, and 0.09 at seventy-two hours, whereas scores for the placebo-treated during the same periods were, respectively, 2.59, 2.55, 2.45 and 2.50. The investigator reported "dramatic and striking" results with DMSO (J. Harold Brown, Seattle).

Somewhat similar results in 1,025 cases of acute conditions were reported by German investigators. There were no side effects more serious than sensations of burning and itching (Heinz John and Gerhard Laudahn, Schering AG, Berlin).

CHRONIC CONDITIONS—Here, respectively, are the numbers of (A) cases, (B) partial remissions of symptoms, and (C) complete remissions of symptoms, and (D) failures reported after two or three months of DMSO treatment:

	(A)	(B)	(C)	(D)
OSTEOARTHRITIS	1641			
spine	896	253	539	104
hip	104	52	28	24
knee	497	202	215	80
small joints	144	46	69	29
RHEUMATOID ARTHRITIS	177	68	74	35
PERIPHERAL VASCULAR DISEASE	57	10	35	12

(John and Laudahn, Berlin)

MUSCULOSKELETAL, ACUTE AND CHRONIC—In 1,068 patients with acute and 848 with chronic disease, DMSO proved effective generally. Beneficial results were unpredictable, frequent and often dramatic, especially in acute conditions. Local irritation was troublesome. The potential for severe allergic reactions should be kept in mind (Christopher H. Demos et al., Squibb Institute for Medical Research, New Brunswick, N.J.).

ANESTHESIA—Tetracaine and other anesthetics dissolved in DMSO and applied to the skin of experimental animals produced prolonged anesthesia, and pain control for five days, without ill effect (Verne L. Brechner et al., Univ. of Calif. at Los Angeles).

ANTI-INFLAMMATION—DMSO, applied to the skin of 500 patients with diversified disorders, benefited 79 per cent. Acute conditions often cleared up completely, whereas long-standing chronic conditions tended to respond well only during treatment and for variable periods after it. Warming made DMSO more absorbent. When the pain was deep-seated—as in discogenic disease and radiculitis—ultrasonic therapy over the painted area enhanced absorption and hastened the response. Favorable responses (as measured by decreased swelling, increased mobility and other objective criteria, as well as pain relief) were achieved in these percentages: acute musculoskeletal injuries (whiplash, etc.) 81.1 per cent; osteo- and degenerative arthritis, 84.1 per cent (while under treatment); rheumatoid arthritis, 77.7 per cent; acute tendinitis and peritendinitis, 94 per cent; acute neuritis (from trauma, shingles, chilling, etc.), 88.2 per cent; acute synovitis and tenosynovitis, 88 per cent; discogenic disease, 50 per cent (poor responses in long-standing cases). DMSO treatment potentiated other drugs—insulin, digitalis, nitroglycerine—making it possible to lower the dosage (Arthur Steinberg, Albert Einstein Med. Center, Philadelphia).

GENITOURINARY—DMSO improved this number of patients: Peyronie's disease, 6 of 13; interstitial cystitis, 2 of

15; epididymitis, 7 of 12; herpes progenitalis, 2 of 5; polycystic kidney pain, 2 of 2; vague genital pain, 1 of 14 (Lester Persky and Bruce H. Stewart, Cleveland Clinic).

RHEUMATOID ARTHRITIS—Only one third of the twenty-one patients treated with DMSO alone or DMSO plus a steroid hormone showed good or excellent response. Many patients did not tolerate the preparation well (90 per cent DMSO in a total dose of 5 to 175 cc). Skin wrinkling occurred after prolonged use. All side effects cleared up (Jack Zuckner et al., St. Louis Univ.).

A carefully controlled study of 274 patients with rheumatoid arthritis sponsored by the Japanese Rheumatism Association showed that 50 per cent DMSO is considerably more effective and has fewer side effects than 90 per cent DMSO. Physical measurements and clinical tests were made periodically. About 50 or 60 per cent of the patients with moderate disease showed very good improvement on 50 per cent DMSO, as compared with about 40 per cent on 90 per cent DMSO. Good improvement was noted in 23 per cent and 16 per cent, respectively, of the advanced cases on 50 per cent and 90 per cent DMSO (Jun Matsumoto, Japanese Rheumatism Assn.).

HEADACHE—Of 154 patients with headache and/or neck pain and cranial neuralgia who applied 90 per cent DMSO to the pain areas several times a day, the results were excellent in 35, good in 60 and poor in 59. Some with two or more conditions, which might or might not be related, found that only one might clear up. Several reported improvement on placebos (Lester S. Blumenthal and Marvin Fuchs, George Washington Univ.).

SPORTS—Of 42 patients treated with DMSO for trauma, 23 were male athletes and 19 male or female non-athletes. Athletes and non-athletes responded in about the same percentages. The most important factor, generally, was time—whether the injury was old or fresh. About two thirds

gave an excellent response, and almost all the rest a good response.

Among the many other conditions treated were: GOUT—Every one of the six patients had complete relief of pain within thirty minutes; DEGENERATIVE LUMBAR DISC—all but one of the 25 patients had a good or excellent temporary response; DEGENERATIVE CERVICAL DISC—10 of 16 patients had a good or excellent response; VARICOSE VEINS 21 of the 22 patients had a good or excellent response; ACUTE SINUSITIS—excellent response in six of the seven patients; THROMBOPHLEBITIS—all three with acute disease had an excellent response and the one with chronic a good result; STROKE—two patients showed unexpected improvement in damage from strokes that had occurred more than two years earlier (M. Marvin Paul, Toronto, Canada).

SPORTS—Eight injured members of the Buffalo Bills football team who were treated with DMSO returned to duty in one half the usual time off for comparable injuries (L. Maxwell Lockie and Bernard M. Norcross, State Univ. of N.Y. at Buffalo).

SCLERODERMA—This is a disease of unknown cause and no cure in which cell death creeps from fingertip ulcers and gangrenous toes throughout the body, calcifying subcutaneous tissues, paralyzing the digestive tract and attacking many organs. Of 42 patients treated with DMSO, 26 had an excellent or good response, with the disease not only arrested but actually clearing up in some of them. Three had returned to normal function and appearance and were able to withdraw—at least for a while—from therapy. DMSO caused a burning or itching sensation in many of the patients for a week or two. A few had nausea and loss of appetite until the dose was reduced. No side effect was considered serious. Among the symptoms which improved greatly or cleared up completely in many cases were gangrene of the feet, ulcers of the fingertips, decreased skin pigmentation, joint rigidity,

tissue calcification, limited motion, pain and stiffness. Results of this sort "never have been observed with any other method of therapy" (Arthur L. Scherbel et al., Cleveland Clinic).

PSORIASIS—After a week or ten days of improvement, "the results were disastrous," and DMSO was withdrawn. Most of the 18 patients exhibited a sudden generalized psoriasis. This was due to "continuous application of DMSO in the concentrations used" (Marvin F. Engel, Brunswick, Ga.).

LEPROSY—Three groups of leprosy patients were treated with drugs dissolved in a DMSO skin wash, along with the oral antileprosy drug, Dapsone. Improvement was rapid and marked (Roy O. Yeats, Sopas Hospital, Wabag, New Guinea).

When Ruskin of the FDA had completed his talk, Arthur Scherbel of the Cleveland Clinic reminded him: "Doctor Ruskin, your group—Drs. Goddard, Sadusk and you among them—reported last week to the Fountain Committee that eye damage had occurred in 24 patients using DMSO. This report appeared in the newspapers. My patients, come of whom I was treating for scleroderma, came to me and said, 'Doctor Scherbel, you tell me there is no toxicity in DMSO, so far as eye damage is concerned, and the FDA says there is.' Dr. Ruskin, one of us is wrong. Would you please elaborate?"

Ruskin said that while there were a few reports of DMSO patients complaining of eye symptoms, no cause and effect relationship had been established. Ruskin didn't mention "the lady in Ireland."

This was perhaps the only time an official was called to account before an audience of scientists or physicians for the widely press-agented contention that DMSO had done serious damage to humans.

When they wheeled her into the emergency room that early February morning, the temperature outside the Rockford (Ill.) Memorial Hospital was 15° below zero, Fahrenheit, and her rectal temperature was 16.6° below normal. She had slipped on ice while stepping out of her car at midnight in front of her home, fallen to the ground, and for six hours lain there.

Dr. Forrest Riordan, former Assistant Professor of Surgery at Stanford University and now an orthopedic surgeon in Rockford, was called.

The patient, fifty-nine, was unresponsive to questioning; she moved frozen arms and legs restlessly, aimlessly. Heavy clothing had given some protection to most of the body, but both hands were blue, both knees a fluorescent red. Ice crystals could be felt in the knee bursae and in all the toes of the left foot and great toe of the right foot; and her feet, like her hands, were an ugly purple. The heart beat irregularly. There was no sensation in any of the discolored tissues.

Conventional treatment was begun in the intensive care unit. The patient, in a gown with protective leggings, was warmed gradually. The rectal temperature rose slowly to 85° at 9 A.M., to 95° at noon and 99.5° at 5 P.M. She was given intravenous fluid and, later, warm liquids, as well as one drug to relax her and another to steady the heartbeat.

The best of conventional therapies wasn't good enough.

About six that evening, large blisters began to form on the toes, and the fingers began to turn black. Riordan applied 65 per cent DMSO from the wrists to the fingertips and from above the knees to the toes.

Since meeting Jacob at a Hand [Surgery] Society meeting in Chicago in 1964, Riordan had treated more than fifty patients with DMSO; and he had seen no side effects more serious than a rash or itch that subsided within an hour. He had witnessed the dramatic diminution of pain, often within minutes or a few hours of DMSO application, in a majority of patients with tendinitis, bursitis, bad bruises, sprains and strains, and even the unsightly injuries from automobile accidents and mechanical crushing.

He recalled that the English used DMSO for cold storage of living mammalian cells, young Charles Huggins' cooling of red cells and blood and Stanley Jacob's preservation of whole organs. Impelling too was the recent demonstration by the Virginia plastic surgeon J. E. Adamson that when a flap was produced surgically in the rat skin, DMSO improved the circulation to it and usually kept it alive. The question was: Would DMSO give new life to the lady's dying digits and restore the blood supply to her limbs?

Ten minutes after Riordan had swabbed DMSO on the patient's hands nad lower legs, the treated areas reddened with the return of blood. The DMSO odor was on her breath, showing that the drug was permeating the woman's system.

On the second day, blisters had popped out on all the frozen areas, and that evening she regained consciousness.

The most cheering development came on the third day: sensation began returning to some of the toes, and later the tips of the long fingers began to have feeling again. By Day 7, she was able to flex these joints.

For an entire month, the patient was sloshed, swabbed and dabbed with DMSO. Almost one gallon of it was used, but side effects amounted only to an occasional rash, a bit of burning or itching (the cause for elation as numbness gave way), the typical DMSO odor, and sloughing of the thawed

skin. During the month the parameters of health returned to normal—body temperature, white blood cell count, sedimentation rate and other blood measurements. By Day 14, it was clear that all tissues were viable; and on Day 17 sensation at last returned to the knees, and only a few scabs showed where the blisters had been. The only other drugs prescribed were vitamins C, A and E.

The patient said that the accident and/or treatment had made the skin on her hands smoother and softer than it had been in twenty years, hair grew and it was rich and darker than before the accident, and her nails lost their earlier tendency to split or crack. By the end of the first year, cold and her first cigarette of the day made her long fingers turn white—a sign that circulation there wasn't entirely normal.

Riordan concluded that the drug should be applied within twelve hours of freezing and that twenty-four hours may mark the critical point for reversing damage to the involved blood vessels.

Frostbite is a common—and frequently a severe—occurrence, oftenest among traffic accident or immersion victims, or drunks. About 55,000 American soldiers in World War II and 7,000 in the Korean War were treated for cold injuries.

Don C. Wood, a biochemist, produced laboratory proof of the usefulness of DMSO in frostbite. He shaved the ears of New Zealand rabbits, dipped one ear of each animal into an alcohol-solid carbon dioxide bath at −42° C., and then treated each rabbit with gauze pads dampened with 1) warm water, 2) 90 per cent DMSO, or 3) 68.4 per cent DMSO.

Groups (1) and (2) received no benefit from the treatment (warm water and 90 per cent DMSO, respectively); the frozen portions blackened in gangrene and fell off. Frozen tissues treated with 68.4 per cent DMSO, on the other hand, survived in many cases in a completely healthy state, and, generally, there was less tissue necrosis, edema and scarring.

When the animals' thighs were subjected to extreme cold, they responded as the ears had.

The most surprising results of all, however, came when

DMSO was used to *prevent* frostbite damage. Tissues painted with either 90 per cent or 68.4 per cent DMSO remained undamaged in cold that brought gangrene and amputation to unprepared tissues.

It was not very long before the FDA's war on DMSO started producing casualties.

Call him Dr. Z. He has had too much publicity—dished up by the FDA in its blacklisting procedure and reported prominently and without question in public and professional media. The coverage did not constitute journalism's finest hour. Nor Dr. Z's. Nor the FDA's.

The FDA charged that Dr. Z had "falsified" his records in several ways: in reporting twenty-four weeks of testing DMSO on prisoner volunteers, whereas the prison records showed only sixteen weeks, and in the number of prisoners. Without knowing the charge, without counsel, or trial by judge and jury, Dr. Z and all scientists associated with him had their names stricken forthwith from the list of those approved by the FDA for testing new experimental drugs.

Dr. Z admitted inaccuracies in his data but contended that the errors were inadvertent and did not influence the final conclusions that the drug was safe. As a full professor at a leading Eastern university and president of three busy commercial laboratories specializing in drug testing, there had been too much detail for one man and a small staff to handle properly.

Dr. Z was fully punished for any careless errors he had made. He had been caught by the FDA, tried (*in absentia*) by the FDA, convicted (*in absentia*) by the FDA, and given an

unusual, and what some might consider, cruel punishment by the FDA—forty lashes in the press.

The way it was handled: FDA Deputy Commissioner Winton Rankin on July 19, 1966, sent out a letter to thirty-odd pharmaceutical companies stating that Dr. Z had "failed to comply with the conditions applicable to the use of investigational drugs"; and he advised them to recall drugs then under his investigation. The FDA used a popular government device, the "news leak," and for reasons hard to understand, the press treated this shoddy story as privileged as though it had come from the Supreme Court or the Congressional Record.

In "reluctantly" confirming the Dr. Z scandal, Rankin made it clear that, with all the damage done, Dr. Z had been apprised of his misdeeds, and he could come now to the FDA and show where the bureau had been in error.

As a supposed finale to this innovation in dispensing justice, the FDA reinstated Dr. Z after he had spent one month in the press-produced purgatory. On August 19, 1966, Rankin wrote to the drug companies that Dr. Z and his associates "have instituted a number of significant changes in their procedures which make it possible for us to now regard [Dr. Z] and the investigators associated with the three named corporations eligible to receive the investigational drugs for clinical testing."

The quality of this mercy was thrice blessed—it blessed Dr. Z et al. who could now face the world ready to find new happiness; it blessed the FDA and its press agents who had established a new and simple system of justice; and DMSO was dead, the FDA had killed it. Again.

Jacob, at the New York Academy symposium, received a message that Goddard would see him the next day in Washington.

I asked Jacob to note what transpired. This is his report:

I met with Dr. Goddard at 5:00 P.M. on the 17th of March, 1966. After a few pleasantries I sat down.

Dr. Goddard looked at me sternly and tapped his hand on the desk, saying, "Dr. Jacob, there are two very serious matters I have to discuss with you. The first is you violated the hell out of these regulations. We gave you permission to treat a couple of hundred patients, and before that circus was over 50,000 patients were treated. I just don't know what to do about all of these violations. We have never seen anything like it. One of the things that bothers me, however, is that I can't find a motive. We know you didn't make any money from your actitivies.

"The second serious point is your accusation that my inspectors went into your personal correspondence files without permission. That isn't the story they told me."

I then related the story of the inspection. His answer was, "That's 180 degrees off the story my inspectors told me."

I said, "Dr. Goddard, did you look over all the material that was photocopied?" He said, "Yes, with the exception

of 40 or 45 sheets of paper, everything seems relevant."

My answer was, "Do you think that there would be anything that was not relevant if I had given them permission?"

Dr. Goddard shook his head and said, "I just don't know what to do about you, Dr. Jacobs. Your violations were terrible."

I had the feeling that Dr. Goddard was saying to me, you forget about the correspondence and I'll forget about the violations, although these words were not actually spoken.

There were strange noises on the telephones. With an army of FDA agents assigned to the DMSO patrol and, reportedly, more agents borrowed from the FBI for this purpose, Jacob and Rosenbaum felt they were under surveillance.

One day, Jacob said, "You know, Ed, until now I had never experienced the sensation of fear."

"Yes," Rosenbaum said.

"Now I know," Jacob went on. "For the first time in my life I know fear. I'm afraid for my family and myself. I'm afraid for doctors and scientists. And I'm more afraid for our country. I can't believe these things are happening in the United States."

Rosenbaum exploded: "Stan, everyone is advising us that the best thing we can do—and you in particular—is to lie low. When the FDA attacks in the press, don't reply; don't antagonize anyone."

Jacob said with rare impatience: "I *have* been keeping quiet. For one entire month, I have not answered the FDA. It doesn't work. More and more, they are slandering me and threatening in the press to prosecute me.

"The Jews in Germany remained quiet; they took the advice: Go along—everything will work out."

Rosenbaum too decided to fight.

When things were blackest, Jacob took comfort from the support shown him by his colleagues in the Department of

Surgery, by Dean Baird, by many others, like Assistant Dean Joe Adams, Dr. William Krippaehne, Dr. Clare Peterson, Public Information Chief Ken Niehans, Bill Zimmerman, head of the business office, Norm David, Chief of the Department of Pharmacology, and Dr. Joe Matarazzo, Head of the Department of Psychology, among them. Elsewhere, too, educators and scientists of stature and integrity were declining to compromise with the FDA.

The strongest support of all came from the patients.

When the FDA banned the use of DMSO, those who had found in the drug surcease from sickness and pain protested. Most wrote to their Congressmen, some to the President or the Vice-President, others to the public through letters to newspaper editors. And some hopefully, fervently, asked the FDA to change its course. Protests came from all parts of the United States.

Here are excerpts from a few of the letters in Dr. Jacob's possession:

> I am a victim of arthritis. For many years I had not known what it meant to be free of pain. I experienced that wonderful feeling when I was treated with DMSO and improved greatly in my ability to move about with normal freedom. I cannot but believe that FDA has usurped power which rightly should be in the hands of medical researchers. It not only deprives victims of disease from blessed relief but it retards the work of dedicated researchers, and our country inevitably will lag behind other countries. [By a medical writer]

> During my career as a medical specialist and medical officer for my country, I have seen many "miracle" drugs—penicillin, streptomycin, para-amino-salicylic acid and isoniazid. Also promazine and chlorpromazine. None of these had the immediate and spectacular results shown by DMSO. Nor did any have the future potential as a

solvent and vehicle for other drugs. My personal experience began in 1964 when I read about DMSO in the local newspaper. I had had multiple bursitis since 1942 when I became so disabled in my right shoulder I could not use a bronchoscope or thoroscope. I had tingling, numbness and blanching of the fingers so bad I could not hold a fishing rod. Fearing I might have Raynaud's disease, I went to the Mayo Clinic. I had had multiple punctures, novocain, cortisone injections, diathermy, ultrasound and all forms of physical therapy with only temporary benefit. I had to support my elbow with pillows in the car and arrange the pillows to permit the "floating" of my shoulder during sleep.

Finally in 1964, when the pain became unbearable, I wrote to Dr. Jacob. Dr. Edward Rosenbaum treated me with DMSO. I took all the tests first. Then 15 minutes after DMSO, I noticed I could hang my arm without pain. Then I began to move my arm in all directions—for the first time in at least two years. I was free of pain unitl October, 1967—for more than three years—when pain recurred in my shoulder. I had used DMSO on burns, and there was no blistering, and no trauma, with prompt relief of pain and swelling. One application over the sinus region completely relieved a headache my assistant had had for three weeks.

We have potent drugs for the cure or control of most cases of tuberculosis; but kanamycin causes neurotoxicity and loss of hearing, viomycin and ethionamid liver toxicity and gastroenteritis, and myambutal occasional reversible blindness. Had these potent drugs been given full treatment by the FDA, as is given now to DMSO, patients with resistant TB bacilli would have to languish in hospitals for years.

I hope my comments both as a patient and physician may help give DMSO the trial it deserves for the sake of the suffering patient. [I.L.C., M.D., F.A.C.P.]

My brother Bob was unable to walk and was bedridden when he read about DMSO. He was being treated for hemophilia, but the doctor, not being sure of the drug and its use, would not prescribe it for him. Squibb referred Bob to an orthopedic man. Because Bob couldn't walk, he went to the doctor's office in a wheelchair. After using DMSO daily for three weeks, he was on his feet again and able to go back to work.

My son, Bill, (also a bleeder) had joint pains and injuries, and I used it on him with marvelous results. We used it for my mother's bad neck burn, the hand which I smashed in a car door, and other matters, and with brief treatment with DMSO these healed miraculously.

My brother used the drug with excellent results until the FDA took it off the market. Perhaps the efforts of the Foundation will not go unheeded. [Mrs. M.H.]

I suffered a disarming attack of bursitis of my right shoulder during a field trip. I drove home with one arm, precariously and with the vibration of my car inducing unbelievable pain.

A friend, Dr. Norman David of the U. of O. Medical School referred me to Dr. Jacob, while my right arm had to be completely immobile by securing my elbow to my hip. Within 20 minutes after the first application of DMSO, a few inches of lateral movement was possible; applications at four-hour intervals permitted 90 per cent recovery on the second day and 100 per cent on the third day.

My experience is a relative inconvenience by comparison to hundreds who have suffered miseries far greater and obtained relief. [C.O.I.]

Early in 1964 my doctors treated my head with DMSO. The treatments, ten in all, healed the severe head pains which I had endured for more than nine years. Up to this

time I had been given many drugs and treatments with no relief at all. [G.M.]

At 46, I was a deformed arthritic mass of pain from a childhood injury which shortened my left leg by healing with a short bend. Physicians thought I had been born with one leg shorter than the other; and this caused a severe curvature of the spine and, with age, arthritis.

Two hours after my first DMSO treatment, I felt a buzzing in my knee and my leg straightened—after 34 years. I then had treatments on my back. My spine is still curved, but nothing like it was. I am straight, my hips and shoulders lateral, not forward with an enlarged hip, and the lump of muscle doesn't show. I no longer have osteoarthritis in my knee and, at 51, I can drive a car long distances and teach a class in college. Before DMSO, I couldn't walk a block or ride 10 minutes in a car.

When I think of all the arthritics—including my mother—and when I think of my sitting at the New York Academy of Sciences Conference on DMSO and seeing the vastly successful indications (medical, industrial, agricultural) presented there, I can't believe what has happened to this drug.

FDA did not attend that conference to find the truth. They were, and still are, hoping for error, so they can justify the silly position they were scared into by the thalidomide crisis.

Please do all you can to see that your committee is aware of the importance of your bill to the health and welfare not only of your own people but to the peoples of the world who rely on you. [Mrs. P.H.J., writer-editor, member of the N.Y. Academy of Sciences]

During the eight months I have been testing DMSO, 1) I have been able to walk and drive a car (I had been consigned to a wheelchair by doctors at the University of

Michigan Medical Center); 2) my terrible swallowing problem due to a calcified esophagus, has improved although I still eat baby food meats; 3) I still have nine fingers left, free so far from amputation. I'm fighting for a change in drug evaluation to give thousands of other people a future of some promise. [J.D.]

I am severely handicapped with a progressive ossificating myositis. It affects the muscles like arthritis affects the joints. The muscles become solid and the joints adamant.

My shoulders, elbows, right wrist, back, knees, and ankles are completely adamant. I have a little motion left in my fingers, left wrist and hips. My care depends on someone else's help 'cause my legs and arms are completely rigid.

My doctor, who I had for the twenty years of my ailment, has tried everything known in his specialized field of arthritis and rheumatism. In 1964, he sent me to Dr. Stanley Jacob to try DMSO. I used DMSO until the FDA put a halt to humans using it. That was one year since I was deprived of using the only medication that has helped my condition.

With DMSO my ailment was arrested and my nodes made smaller. I suffered less pain.

I have wrote the FDA, Dr. J. Goddard, about my case asking them to please release to my doctor some DMSO. Since the ban my ailment has progressed to a much more distressing condition than in 1964, before I started using DMSO. They have made no attempt to try and help my case. [K.L.W.]

I am the victim of a rare chronic systemic virus infection, which is not recognized by a majority of the medical profession. In 1965, I had an acute attack of encephalitis, hepatitis, and asthmatic bronchitis so severe that mental and speech coherence were impaired and I scarcely hoped

to live through the night. The internist who had accepted me three months earlier gave me prednisone, which resulted in immediate improvement. But before the course was completed, serious symptoms of encephalitis recurred. I felt I had nothing to lose, as the next attack would almost certainly be fatal.

I tried DMSO strictly on my own responsibility. Results were truly dramatic. All symptoms diminished, and after an absence of six weeks I returned to work. Laboratory tests showed equally dramatic chemical improvement in liver and white cell count.

When I returned to work, the FDA halted all clinical testing of DMSO as eye lesions had appeared in laboratory animals given massive doses for six weeks or more. Being unwilling to sign false statements to obtain DMSO ostensibly for laboratory use, my condition deteriorated. Appeals to the FDA—whether directly, or through the federal agency where I am employed, or through members of the Senate and House, were of no avail. After much searching I was able to procure some DMSO in a nearby country. But when I had only two months of this supply left, I could obtain no more.

To preserve my life, I was forced to become either an expatriate or a smuggler. Since I could not earn a living abroad, I was compelled to adopt the latter course. It cost me a fortune.

I have been a law-abiding citizen, having been charged with nothing more serious than about six traffic violations during 40 years of driving. Because of the unconstitutional actions of the FDA, I have been forced to violate valid and necessary Federal laws in order to preserve my life. I believe this constitutes a very serious infringement of my constitutional rights, and, as such, is a matter of concern to the ACLU.

Since it is almost hopeless for an individual of modest

means to challenge a Federal bureau in the courts, I respectfully request legal aid from the ACLU:

1) To seek an injunction barring FDA from search and seizure and other interference with *my* existing supply and medical use of DMSO;

2) To bar FDA, Customs, or the Department of Justice from prosecuting me for violations to protect my life;

3) To permit me to purchase DMSO to control my disease, subject only to a licensed physician.

Thousands of patients with crippling diseases and with diseases of progressive deterioration, ending with 100% assurance of mortality, are denied lifesaving DMSO by bureaucratic inertia and prejudice on the part of the FDA. [A.B.C.]

I attribute *all* of my success to DMSO for not having to go through with the amputation of my right leg. I was told by several professional men I would not be able to stand the pain otherwise, and they were right. The pain was so excruciating, so severe that I bounced my head on the wall. I had to crawl instead of walking, and I took 15 to 20 painkiller pills a day.

With all this in mind, I was brought in a wheelchair to see Dr. Jacob. Thank God for that day. From that day on, I began using less and less pills, until there was nothing but DMSO. I walked, did my own shopping, my own housework.

For two long years this wonderful drug has been kept away. How many people have lost their limbs during this time? Tying the hands of Dr. Jacob in my estimation is an unforgiveable sin. Please, please let DMSO come back to us. [E.M.F.]

No lovelorn swain, no homesick soldier in a faraway jungle, no starving student looked forward to the postman

more avidly than Stanley Jacob did. Through his mail he learned which battles he was winning, which losing, and how went the war on its multitude of fronts—with the FDA, in Congress, with the plethoric pathology that beset his patients, with organized scientists, individual doctors, with creditors, with admirers and critics.

The mailman endowed Jacob with the gift of total ubiquity—the vicarious power of being everywhere at all times.

Fortunately, Jacob was a fast reader. A glance gave him the contents of a page. He was rapid at dictation. Usually he could absorb his incoming mail and dictate a few dozen letters in a couple of hours.

Jacob's day was long and busy. It often began in the middle of the night with emergency surgery. Four mornings a week, between about eight-thirty and noon, he was either operating or in the clinic seeing patients scheduled for surgery. He himself seldom saw more than twenty of the fifty or sixty patients reporting to the surgical clinic; but in the clinic he instructed medical students in diagnosis and treatment. The twenty-eight beds in the state-operated medical school surgical ward were occupied by patients beyond the expertise of most surgeons or the procedure called for equipment unavailable elsewhere. The University of Oregon Medical School long had been famous for its surgical teams; its students saw many rare surgical problems and performances that they never again came upon in their careers as surgeons.

Jacob's day was crammed with administrative duties, animal research, visits with surgical patients, a course on one day for each of six weeks for twelve to fifteen seniors on the fundamentals of operating room behavior—aseptic conditions, tying, handling surgical instruments. Using one dog for no more than one single surgical procedure (after which it is "put to sleep"), he had the students insert a tracheotomy tube into the neck, explore the interior of the belly, suture a

nerve in the neck, take out part of the thyroid, hook up sections of the digestive tract, and, in the final session, divide the great aorta leading from the heart and sew it together again.

Two nights a week, Jacob treated fifteen or twenty patients with DMSO. At this rate, thirty or forty a week, he had given more than four thousand treatments with DMSO by 1972.

Some of the most bizarre conditions were seen at his DMSO clinic. Many patients became his friends and corresponded with him for years. He seemed to bleed a little with those he couldn't help and die a little with those who came to the end of the road.

There was, for instance, a case of myositis ossificans generalis, which is so rare that some voluminous medical references fail to list it. Furthermore, they might just as well ignore it; there is nothing the patient can do except die. Slowly.

A man in his thirties had had the disease for twenty years. In 1964 Jacob started him on DMSO, and after a few months (of topical application) he had improved. When they had started out, a good deal of his body had calcified—he couldn't move any of his joints; he couldn't lie, or sit other than rigidly; he couldn't bend his neck or move his fingers. His knees, his hips, his ankles—all were rigid. But he could open and close his mouth; so he could eat, and, for the time, survive.

"We concentrated on his shoulders," Jacob told me, "because I felt that if we could get a little motion in the upper part of his body, it would make him less of a vegetable. After a couple of months, he did recover some shoulder motion. Then, gradually, some of the calicifed soft tissue lumps became smaller and smaller.

"When the FDA halted studies in November 1965, the young man had regained much use of his fingers; he wrote, literally, hundreds of letters—to the FDA, the Congressmen,

and to the President. The FDA sent him stereotyped letters. The President, who receives a lot of touching appeals every day, overlooked this one.

"In time, special permission was given to the doctor to resume treatment. Naturally, the patient would have to submit to frequent, time-consuming and financially debilitating tests."

Other diseases were equally baffling but a good deal more common. One was Lou Gehrig disease, or amyotrophic lateral sclerosis; Jacob treated a neighbor of mine with DMSO and wrought some instant, overnight and slightly delayed wonders of therapy. But from my own knowledge, he was never permitted to pursue this line of investigation; my neighbor's physician forbade DMSO.

One patient with multiple sclerosis was about twenty-nine when she came from another state to Oregon for treatment for the virulent disease. Not only was she paralyzed, but she also suffered from kidney failure to the point that she was trying to induce those operating the University of Washington dialysis program to save her. At this time one could be saved for perhaps nine who had to be rejected for help on the artificial kidney machine.

Jacob started the MS patient on a high dose of DMSO, two ounces a day—but dabbed on. Then, with great daring, he and his associates gave the DMSO orally—a stiff dose in tomato juice or orange juice.

"Her improvement was dramatic—as dramatic as any benefit I have ever seen," Jacob told me. "Within a week her renal problem seemed to come under control. Then—after a few more weeks—she walked again.

"Now, six years after her first DMSO treatment, she still has wobbly knees. But she walks. She drives her car. She takes care of her two children and her husband. But she is going downhill. I wish we could help her again, but we just don't seem able to. Despite this, however, I am not convinced that DMSO alone is useful in multiple sclerosis."

Marge Davenport of the *Oregon Journal* engineered what she hoped would be a practical solution to Jacob's problems with the FDA. She persuaded Congressman Robert Duncan of Oregon to bring together in Washington representatives of both sides—the FDA and DMSO advocates—and let them thresh out the issues in the presence of the press.

On October 5, 1966, the entire cast gathered around the conference table. Duncan was referee. On the side of the government were Goddard, Hodges, Ruskin, Dr. Milton Silverman (representing HEW Secretary Dr. John Gardner) and FDA press agents. On the scientists' side were Jacob, Dr. Lester Blumenthal of George Washington University, who had found DMSO effective against headache and neuralgia, Dr. Arthur Scherbel of the Cleveland Clinic, who has used DMSO as an effective treatment for heretofore untreatable scleroderma, Dr. Marcus Mason of the Mason Research Institute, Worcester, Massachusetts, who had reported DMSO remarkably non-toxic in animals, Dr. Dan Gordon of Cornell Medical School, who attested to DMSO's efficacy in some eye diseases and to its lack of toxicity to the human eye, and Dr. J. Harold Brown of Seattle, and the dean of American pharmacologists, Dr. Chauncey Leake.

The press was not admitted during the discussion.

Goddard and Hodges opened the session and dominated it. They dwelt at length on the supposed toxicity of DMSO.

Jacob told me later, "No one at the meeting spoke up. We wanted the FDA to save face and get off the hook gracefully."

Jacob said that when he started talking about DMSO's use against conditions which could not be treated well by other means, Goddard cut him off with the observation that he was a highly prejudiced observer.

Jacob gave me this account: "I suggested that some of the differences between the scientific community and the FDA on DMSO could be resolved by the National Academy of Sciences. Dr. Goddard replied that the suggestion was very similar to one advanced by Dr. Andrew Ivy during the Krebiozen matter."

The press was called into Duncan's office and once again, Goddard took over. "He answered all the questions," Jacob told me. "There wasn't much opportunity for any of the investigators to say a word."

"What did you do?" I asked.

"I talked to the reporters outside the office—after Goddard had gone," he said.

Because crusades, for good ends and bad, cannot be conducted successfully in Washington without the aid of a professional and costly lobby, DMSO's legislative support proved weak and ineffective.

The Oregon delegation—especially Senator Mark Hatfield and Rep. Wendell Wyatt, both Republicans, and Rep. Edith Green, Democrat—worked heroically for DMSO. They had arranged for the Library of Congress to reproduce and translate any DMSO scientific papers published abroad.

Wyatt conducted a series of rebukes to the FDA on the floor of the house. The orations appeared in the Congressional Record under the standing headline, "DMSO, the Persecuted Drug." When Goddard's agents were most active, Wyatt said:

"Thousands of people in this country are needlessly suffering because of the FDA's arbitrary holdup of clinical

testing of DMSO. The holdup is pure futile arrogance on the part of a Government agency.

"In thousands of documented cases, suffering has been alleviated, pain reduced, and symptoms have disappeared; but in not one single case had a serious side effect been discovered. Restrictions on its use make companies and doctors alike shrink from even filing an application to test this drug. FDA actions have been so harsh, in fact, that drug companies refuse to make DMSO available in medically acceptable grade. The FDA has been accused of bludgeoning the medical community into submission . . . of forcing submission to its orders by blacklisting investigators, threatening scientists with unwarranted court action, conviction by press release and, in general, using questionable methods to control the actions of the medical profession."

Thanks to the Oregon delegation's intervention, the Library of Congress at this time began supplying Jacob with reprints and English translations of DMSO papers in foreign journals.

The first two were by groups of Italian dermatologists. Here are my abstracts of them:

A cream containing an antibiotic (neomycin sulfate) and a cortisone-type hormone (9-a-fluoroprednisolone 21 acetate) was divided into two batches: Batch A, containing DMSO, and Batch B without DMSO.

Batch A was applied to eczema and dermatitis sores on the right sides of 24 patients, and Batch B to sores on left sides of the same 24 patients. Treatments ran from 2 to 20 days. Based on the rapidity and completeness of healing, results were graded excellent, good, or incomplete.

Batch A—containing DMSO—was superior to Batch B in 16 cases, inferior in 2, and the same in 6. [Prof. F. Serri, University of Pavia, *Minerva Dermatologica* 41 (1966)]

Combinations of DMSO, the cortisone-type hormone, triamcinolone acetonide, carbopol, and propylene glycol were applied to 90 patients with various skin conditions.

Prof. Bella found that the combination, with considerable consistency, proved far more effective against most of the skin conditions than the cortisone-type hormone alone. Various combinations often yielded excellent results in such conditions as eczema and psoriasis.

With DMSO serving as a vehicle to transport it into the deep skin layers, triamcinolone acetonide doses could be cut to 10 per cent of normal; and except for the typical DMSO odor, taste, and brief burning sensation, the drug was well tolerated, and without ill effects. [S. Bella of the Dermatological Hospital Institute of S. Maria e S. Gallicano, Rome; *Minerva Dermatologica* 41 (1966)]

Jacob read the papers with interest—and also with a touch of sadness. He wondered whether he would continue to receive reprints from aboard. Or had the FDA quenched research with DMSO throughout the entire scientific world?

The third international symposium, November 8 and 9, 1966, in the elegant old Palais Pallavicini in Vienna, was sponsored by the University of Vienna Medical School and financed by the German drug house Schering AG. It attracted 150 scientists from twelve countries.

Leake, as keynoter, said, "Rarely has a new drug come so quickly to the judgment of the members of the health professions, with so much verifiable data, from so many parts of the world, both experimentally and clinically, as to safety and efficacy.

"Fortunately, members of the health professions throughout the world are not all bound by the bureaucratic regulations and judgments of the U.S. Food and Drug Administration."

It was strange hearing this statesman of science in this hall and this city, which less than a generation ago had been

occupied by one of the bloodiest regimes in all history, now aplogize for regimentation in America.

As at the Berlin and New York symposia, scientists said they had failed to induce eye damage with DMSO in any animal species close to the human, and they could find no evidence of eye troubles attributable to DMSO in any patient.

They reported that under certain conditions DMSO would a) overcome edema and other effects of trauma; b) carry the anticoagulant heparin through the skin and into the bloodstream; c) sharpen tests for kidney and liver function; d) damage the bore of arteries and veins when injected into them in concentrations higher than 30 per cent; e) reduce body water and both sodium and potasssium (90 per cent DMSO, topically, increased urine volume ten-fold); f) with compound 48/80, DMSO prevented the calcifying effect of metal salts like lead acetate, and when DMSO was applied to the animal skin prior to giving 48/80 it preserved mast cells—treasure-houses of anti-coagulant and anti-inflammation chemicals—in injured tissues; g) given to mice ten days before infection, DMSO prevented typhus; h) it tended to solubilize collagen, a possible anti-aging effect; i) and in very preliminary observations, DMSO seemed to make resistant tubercle bacilli vulnerable to drugs—subsequent studies cast doubt on this effect, however.

In human studies—many controlled—DMSO reportedly a) relieved pain and sped healing; b) cleared up headaches associated with cervical disease or shoulder-hand syndrome; c) benefited 77 per cent of patients with rheumatoid arthritis and 84 per cent with osteoarthritis; d) transported the anti-cancer drug 5-FU and anti-viral 5-IDU through the skin; e) helped scleroderma patients in controlling contractures, calcinosis and skin manifestations; f) offset some injurious effects of cobalt radiation therapy; g) proved superior to all other therapy for winter and other sports injuries; h) controlled many kinds of pain, including that associated with blood clots; and i) cleared up benign skin growths of the

eyelids and neck by dissolving the oil fats which caused them.

Scores of scientists had confirmed the majority of the claims Jacob had made; and some had added new and original claims of therapeutic values. Jacob felt vindicated at the end of the symposium. The distinguished scientists clustered around him, shook his hand, congratulated him for what some called a classical contribution to science and medicine.

The entire assemblage seemed in a happy mood. All except one—Bob Herschler, who said not one word to Jacob or Rosenbaum or Leake. He stood aside alone and in silence.

At the Vienna conference it became known that Germany, without fanfare, was restoring DMSO to the drugstore shelves. There were more than adequate safeguards. It was a prescription drug, limited to topical application for specific ailments. It could not be applied for more than fourteen days at a time to anyone and under no circumstances to pregnant women. Germany became the first of a gradually growing number of countries who became disenchanted with the United States Food and Drug Administration and who quietly made DMSO available to doctors and their patients.

The three classical approaches to the development of therapies are: 1) empiricism—the trail-and-error testing, with or without a rationale, in hope of effecting a cure; 2) serendipity—the chance, or fortuitous, discovery by the alert and prepared mind; and 3) the biochemical, or orthomolecular, in which a specific compound is used to correct a known chemical defect.

Jacob had adopted all three approaches.

Once he had satisfied himself that DMSO was extremely safe and remarkably effective against an assortment of conditions, he experimented boldly and empirically against many other diseases.

And when a chance observation suggested that DMSO

might prove useful against new diseases, he lost no time testing it. Like the legendary Three Princes of Serendip, who sought one thing and found another of even greater value, Jacob treated one disease and discovered that DMSO tended to cure another in the same patient.

The story of Nate Amato illustrates serendipity.

Back in 1916 Nate and some other kids had built a fire over a handful of dynamite caps they had found in an empty house. They lit dry sticks and scattered to wait for the explosion. When nothing happened, one of the older boys said, "Nate, go over and see what's the matter." As Nate bent over the fire, the caps went off, and the dirt and rocks crashed against his face.

The left eye had to come out. And the right eye gradually deteriorated. Three years after the accident Nate dropped out of school because he couldn't read or even see the blackboard; and eventually he couldn't distinguish light from dark. He bought a filling station and, even though blind, got along all right.

Nate heard that one of his customers, Dr. Jacob, was experimenting with some magic stuff called DMSO; and one day when Jacob stopped for gas, Nate asked, "You think DMSO might help this eye that I've got left but can't see out of?"

Nate had been blind for more than thirty years. Nevertheless, Jacob told him to bring a complete report from his eye doctor to the lab on Wednesday evening. Nate did and ever since then he has visited the lab on Wendesday nights—always first in line. He comes a little early, bringing Jacob a hamburger sandwich drowned in Tabasco sauce, because Jacob doesn't have time for dinner on the nights he sees DMSO patients.

Nate has not regained any vision; the only thing that's different since he started applying DMSO to his scalp and then by eyecup, first over the lid and then to the eye itself, is that he has a sensation of flashes. The intensity varies; the

flashes are brighter on sunny days than on cloudy days.

One day Nate noticed a remarkable thing: running his fingers over his bald head, he detected traces of very fine hair growth—like peach fuzz, only maybe a little sparser. He felt that he knew the answer; Jacob had told him that one of the effects of DMSO was to dilate, to open up, the fine blood vessels in the skin, and it now was obvious to Nate that with a new nutrient supply, the follicles were producing hair where hair had not been growing for many years.

It was to be expected, of course, no one would credit the story of DMSO's growing hair on a bald head. Nevertheless, Jacob applied DMSO regularly—or prescribed it—to five more bald men. Hair of sorts, grew on all the bald heads—a fine fuzz that appears in the scalp areas where hair last grew and then spreads to other sites in inverse order of its disappearance during the balding process. Ed Rosenbaum was one of the five with some evidence of returning fuzz, but he still was not convinced that DMSO was responsible.

Nate once had a whiplash injury which his doctor felt triggered an arthritis attack; the x-rays showed degenerative arthritis in his right hip. "I began applying DMSO a year later," he said, "and I haven't had any trouble ever since." Nobody calls him cured, of course.

Amato is a down-to-earth, unemotional sort of fellow. Diagnostic x-rays confirm his arthritis story, and a series of snapshots show the growth of hair, very slowly, over several years.

He tells this story of his enlarged prostate:

> It could happen with age, I guess. I was having to get up a couple of times during the night. I was developing pressure in that area.
>
> Before this I was being treated by a doctor at the Portland Clinic; and I'd gotten to the point where the doctor suggested that I should have an operation for an enlarged

prostate. I put it off and asked Dr. Jacob to see what he could do. My doctor told me to try it if I felt like it.

Dr. Jacob tried DMSO with a series of prostate messages. The pressure disappeared. I no longer had to get up during the night; I sleep until six-thirty or seven-thirty in the morning without having to go to the lavatory. I have no discomfort whatever. That was sixteen or seventeen months ago. I still get treated occasionally. But that condition is under control.

Jacob told me that a physician in Texas some years earlier had reported injecting DMSO plus progesterone, the "pregnancy hormone," into enlarged prostates and that biopsies, examined under the microscope, indicated a return toward normal.

Vision never did return to Amato's eye.

Jacob took some satisfaction from the effects of DMSO on Amato's bald head, arthritic spine and enlarged prostate. But he felt a keen sense of frustration that DMSO could do nothing for his blindness. The sensation of flashes that Nate reported, however, made it impossible for Jacob to abandon the idea that DMSO might help in some kinds of baldness.

Harry E. Palmer had spent most of his adult life in the field of public health. Up to the time of his retirement, he had been a lay psychologist for the state of Oregon.

Palmer and his wife had been diagnosed as having osteoarthritis. Mrs. Palmer's condition had become chronic. To open her hand with the locked finger, she had to reach around with the good hand and pry the bad one open. Harry had always been a little crippled as a result of old injuries; but it was only after he started laying tile in his retirement home down near the Oregon coast, that it really hit him.

"I got to the point where I could hardly walk up those thirty-five steps that led across the terrace from the street and

up to the second floor bedrooms," he told me. "I came to know each one of the steps individually—as a challenge."

When Harry was on top of a twenty-five-foot ladder painting the house, his knees gave out. He stopped dabbing at the gable and climbed back to the ground—painfully, carefully.

Harry's mother had been one of the first patients treated in Jacob's lab six or seven years earlier; and ever since then, periodic treatments had kept the terrible pains in her knees under very good control. So Mr. and Mrs. Palmer asked Jacob to treat their arthritis.

"Dr. Jacob sat and talked with us for about an hour and a half, and then he accepted us for his arthritis program," Harry told me. "I just brushed the DMSO liberally around my knees and my hands with a camel's hair brush. My wife dipped her hands in DMSO.

"The treament was excellent for my wife's hands and fingers. Now there's hardly any deformity at all. As for me, within three months I was able to run up and down those thirty-five steps.

"It is a new life for both of us."

During one conversation, Jacob said, "Harry, how would you like to try for a new head of hair—natural hair?"

Jacob showed Palmer some before (bald) heads in pictures and snapshots of the same heads, now not so bald, after several months and years of DMSO treatment.

"I didn't hestitate," Palmer said. "I signed right up."

"I now have fine hair on the back of my head almost an inch long; and it may be starting to come back in other areas too. However, it will take years for me to develop a decent head of hair."

Once again, serendipity intervened, and Harry Palmer's eyes became the beneficiary.

When he was ten years old Harry had roller-skated downhill and was hit by an automobile. He was unconscious for two days and not expected to live. When he was able to, he started reading a book, rubbed his left eye and screamed out,

"Mother, I'm blind." That was when he realized the sight was gone completely from his right eye.

The ophthalmologists said nothing ever could be done for the right eye, and they predicted that Harry would lose the remaining sight in his left eye within six months. Thanks to the perseverance of one of them, however, some vision was preserved in the left eye. The right eye was sightless—dead; it wouldn't even focus.

"After I had used DMSO on my head for baldness for a few weeks, I began to have a strange new sensation back of my sightless right eye," Palmer told me. "I can't say it was pain, but it wasn't comfortable. It was sort of a dull ache.

"Oddly enough the left eye—that's the one that still had some sight left, not much but some—wasn't affected at all.

"Dr. Jacob had often advised us to tell him of anything unusual, so I told him about my right eye. He asked me if I'd be willing to go ahead with an experiment and bathe my eye directly in DMSO. I told him of course I would.

"We tried DMSO in various percentages. It caused quite a reaction. It stings for several minutes before it subsides, and tears run as when you get something in your eye. The eye is bloodshot for fifteen or twenty minutes, and the reaction lasts maybe a half-hour."

One day in Jacob's office, they blindfolded the left eye; and with only vision from his blind right eye, Palmer was able to describe objects that Jacob held at a distance. Then, faltering somewhat but without bumping into anything, he walked around a strange laboratory.

From that point on, Palmer's progress was fast and life was exciting. His pupils accommodated to light; his eyes focused; and then there was the supreme thrill—he could detect color (something he had not been able to do since before his accident) and name each shade correctly.

Jacob decided to test DMSO on an entire series of patients with "incurable" nerve blindness.

Late in May 1967, I carried my tape recorder into Goddard's big, shiny new office in the big, shiny new building, furnished in the modern manner of the fat and happy government of an affluent society. There were handsome trophies here and there—gifts from celebrated admirers in exotic areas of the globe.

My interview, with Goddard, assisted by an aide, Dr. Robert Hodges, ran for more than two hours and the transcript covered thirty-five pages of dialogue, single-spaced. It started off pleasantly. Goddard said, amiably enough, "You never saw two Irishmen who didn't want to get into a discussion, did you?"

I said, "It's usually in a saloon, though."

He said, "Sorry about that."

I pointed out that scientists at the New York and Vienna DMSO symposia were almost unanimous in citing the drug's fine therapeutic effects and minimal side effects.

"This is not our information," Goddard said. "I think we hear from different parts of the scientific community and I think this is quite natural. Advocates of a position often tend to go to meetings and present their experiences with a drug.

"Just last week a physician here was very enthusiastic about a limited use of DMSO. He found that by mixing the drug with a local anesthetic he gets a much better anesthesia than he does with any other single agent. It enables him to perform certain surgical procedures that otherwise are very different and have an element of danger connected with them.

"But the point of interest was that he brought with him some toxicity studies that I hadn't seen heretofore. These were carried out on the West Coast in association with a university center. As I recall, six of the ten devloped leukopenia with administrations of small amounts of DMSO. Now, leukopenia—we view decreases in the white cell count as serious, and these were in the order or magnitude of three thousand white cell decreases from the normal.

"The striking thing was that there were eight patients out of ten who showed drops. [To Hodges] How did that go? It was six of eight ultimately, wasn't it?"

Hodges said he didn't know; he wasn't present. He did say that the white counts returned to normal, and the scientist was halfway through a rerun when all experiments with DMSO were terminated. Hodges said he "assumed" that at this point it was three of the patients who again were showing leukopenia.

Goddard said that, although he was familiar with the general DMSO literature, "Who was aware of this? I submit, some of these kinds of reports haven't received the study and attention of the general community."

Within the first few minutes of our interview, in his impressive presentation, Goddard was inconsistent himself at a time when scientists committing comparable mistakes were wrongly threatened with criminal action and disgrace.

I wondered too at his acceptance of a sketchy white cell depression as a critical situation. Some might wonder whether the agent might not be worth testing against leukemia, which is characterized by too many white cells.

Neither Goddard nor Hodges could identify the scientist immediately. I came across him later and found that his story varied considerably from Goddard's, as we shall see.

Despite the vagueness of his facts, Goddard expressed enthusiasm for the toxicity he felt he had discovered. He said it was "fascinating—one would not have expected this kind of dose response. Intriguing! And the consistency with which it occurred!"

"Now, a lot of comments have been made about the eye problem," Goddard said. "How do we really know it's only in animals? As I recall, there have been only seventy-one individuals in whom follow-up eye examinations have been carried out—out of the many thousands of people who received the drug when it was being distributed so widely."

Again, Goddard's figures were at variance with others'.

(More than 600 such cases had been reported at this time.) I asked him, "How many patients do you have eye reports on who have been taking aspirin?"

"With any drug, when there is a suggestion of a problem based on animal studies or clinical observations, we insist on additional studies in humans," he replied. "Now, I know of no animal studies citing difficulties with aspirin."

I reminded Goddard that aspirin's toxicity was real and had been widely reported.

With considerable cutting, the interview covered such points as:

GODDARD Every drug has its toxicity. Now, I think we've demonstrated time and time again with our new drug approvals during this past year that we're not sitting here to block good therapeutic agents from coming into the marketplace. Rather, we're here because there has been a job placed upon us through the scientific community and Congress.

I You've frightened investigators to death. One gave up on DMSO in his blood-freezing technique. He told others—not me—it was just too risky to use.

GODDARD Let's put a little of the responsibility on the people who acted in an irresponsible fashion. We had a tough job of taking the action, that's true. But by the same token, those who acted so irresponsibly caused this action to take place.

Now, there's no question that we now have enough information that we are evaluating and looking at to consider changes in the policy statement which would broaden the testing.

I think we're very close to coming up with a policy statement that will open up studies.

I Are there as many as fifty patients in the United States being treated with DMSO?

GODDARD Yes, there are.

I Where are they?

HODGES I can tell you. They're throughout the country. There are about sixteen investigators and should imagine about fifty or sixty patients receiving the drug. These have all been followed very carefully. We're doing now what the investigators should have done three years ago. We are completing Phase Two, the evaluations of late safety, Phase One and Two, in human beings.

I You are aware of the letters from patients and their families stating that the patients are in enormous pain which cannot be controlled by any means other than DMSO. What is your attitude, Dr. Goddard, to children who must live in pain?

GODDARD Well, first of all, in all cases where the physician wrote us, we have evaluated each of these on an individual basis and then we took action accordingly.

HODGES Dr. Goddard delegated to me the deciding of whether or not an application should be approved in conditions where there is pain or the patients have to be on narcotics, where they have life-threatening conditions. Scleroderma is one we are all well aware of. If they have severe pain from rheumatoid arthritis that was crippling and are not responding to anything else, I would not refuse approval. In fact, I don't know of any cases offhand where I have refused approval. I can't name one.

I If I said I had seen letters to the effect that you had either refused or made availability of the drug impossible—

GODDARD Well, let's clearly define what you mean by making availability impossible. We will approve an individual's request and then he must obtain a sponsor.

HODGES Yes, and it's still a study, even though they're treating a patient who is seriously ill. It must be carried out with full regard for the patient's safety. They have to do these eye studies and blood studies to show there are no effects on the marrow, liver and kidneys. There is nothing to stop any practitioner who is sufficiently motivated. These studies cannot be done by the average general practitioner.

I If it's so simple, how do you account for so little use of DMSO in patients who need it?

GODDARD First of all, many physicians aren't willing to carry out the studies required for Phase Two.

I Could another reason be that the physician then becomes subject to visits, let's call them, by plainclothes policemen, armed—

GODDARD I take exception to that. Our investigators are not armed. We request our FDA field staff, our inspectors, to visit scientists and obtain certain data on their usage of DMSO—and their accountability for the amounts they'd received and used. This was done after a congressional hearing.

I What happens if the researchers decline to make the records available?

GODDARD Then we have to go to court and ask for a subpoena.

I Have they entered laboratories in the absence of investigators and gotten records?

GODDARD They have never obtained records without permission of the investigator. In one instance the investigator couldn't be there during the entire visit, because he was greatly involved in shipping DMSO to persons around the country. He told his secretary to provide them with the records. The university in that same instance also instructed the person involved to turn the records over to the FDA inspectors.

This has been looked into very carefully, because some allegations have been made that we have acted improperly. We're prepared to defend our inspectors' activities on this.

I Have your inspectors entered laboratories and physicians' offices without an appointment?

GODDARD Not without permission.

I What kind of permission?

GODDARD Go to the person in charge and identify themselves—tell them the purpose of their visit and what they are seeking.

I But they don't make prior appointments?

GODDARD They try to.

I They do try to?

HODGES Not always.

GODDARD They try to in many instances.

I If someone quoted your agents as saying they were required to enter the physician's office without prior notice, would that someone be lying?

GODDARD That would depend on the circumstances.

HODGES Many of our inspectors go to the physician's office and say, "Here we are, and this is what we want to see."

GODDARD But they identify themselves—and do not enter without permission.

I Despite its [DMSO's] willy-nilly use, uncontrolled, on eighty thousand or more people, so far as is known it has been without a single serious side effect.

GODDARD Not so far as is known. Who followed up on the people? Who checked up on them? There has been reported at least one instance of anaphylactic death.

I The lady in Ireland?

GODDARD Yes.

I She was taking several things. Are you familiar with the circumstances?

GODDARD Yes.

I And you still say that?

GODDARD I say there is one case reported. Now look, this is why facts are needed.

I mentioned that I had heard from Dr. Z, who had been blacklisted, libeled and slandered, before being reinstated. Goddard said Dr. Z "has proper recourse if he feels he's been damaged in a fashion that's not appropriate. He can take this to the courts and sue us and sue me. If he's willing to do that, I'm perfectly willing to go to court on it. There's no problem there."

I had been denied data on DMSO from his office on the grounds that the facts were "confidential." Goddard commented: "That's quite appropriate—part of the policies we operate under. And I must say these are known to Congress too."

Regarding the quality of FDA scientists, Goddard said there were some good ones, but "like any organization, we have all gradations."

I told him he had been criticized as a czar of medicine with only one or two years in private practice and, reputedly, "without a very distinguished record."

"Nobody ever came to evaluate the quality of medical care I dispensed in my practice," he said. "How can they make that evaluation?"

I told him the critics were speculating.

"That I wasn't successful?" He responded with considerable spirit. "That I couldn't make a go of it? Let me tell you that last year for the first time, my salary equaled what I was making when I quit the practice of medicine in 1951.

"I submit to being in practice for fourteen months [in Kalida, Ohio] and grossing over twenty thousand dollars a year. You're not unsuccessful when you're charging two dollars for an office call (including medication) and twenty-five for an obstetrical case (prenatal, delivery and the medication). It was a very busy practice, if that's a measure of

success. In fact, that was the reason I quit. I didn't want to devote eighteen to twenty hours a day and have to practice in a fashion that I didn't think measured up to my own standards. I don't think that seeing forty to fifty patients a day and delivering up to a hundred babies in the last twelve months was exactly a good brand of medicine."

As for his being a czar of medicine: "I think that charge is ridiculous on the face of it. We don't have the ability to handle the practice of medicine in this agency.

I asked whether Goddard made mistakes, and he said, "You can't be an activist type of organization and not make mistakes." I asked what kind of mistakes he had made in the last year, and he said he had made some poor placements within the FDA. He added that he would have handled the vitamin controversy differently. (In this case, the FDA was caught attributing to the National Research Council the old FDA fetish against vitamins—proposing to complete the labeling of vitamin bottles with an announcement that people got enough vitamins normally from the food they ate. The council made the FDA recant.)

Apropos of Goddard's admitted mistakes, I asked whether he thought it fair to prosecute Dr. Z and others. Did it seem that for him and the FDA to err was human but scientists' bookkeeping mistakes were criminal offenses?

"To err is human," Goddard said. "But to submit false data, which is not an error, is not human."

Reputable investigators had presented data at the Vienna meeting on more than ten thousand cases treated with DMSO which the FDA was ignoring; the cancer findings alone were urgent enough to be checked, I suggested.

"With cancer," Goddard said, "during this period, we stood prepared to receive and approve any protocol on the treatment of cancer. Did we receive any?"

"No," said Hodges.

I asked, "Doesn't it make you wonder why you didn't?"

There was no direct answer.

Goddard complained that the DMSO story appeared first in the public press.

I pointed out that he and the FDA were having a terrible time keeping things from the press, that somehow news did get out of his office into the papers and on radio and TV.

He confessed that news leaked out of the FDA. "There are leaks everywhere," he explained.

Goddard insisted that the FDA was merciful: instead of taking an erring scientist or doctor into court, it merely blacklisted him.

"A lot depends on the nature of the individual case," he said. "We make that assessment, and we always meet with the investigator, give him an opportunity to come in and show us where we've been wrong. So far this has been a workable system."

Was it fair to listen to the man's story *after* destroying him? I said, "Well, it's been workable from your point of view. But take the investigator whose reputation is shot, his career is over. No one again will trust him after a trial in the press initiated by the FDA."

Goddard heatedly denied that the FDA initiated a "kangaroo court in the press."

It was Hodges who finally explained the practice:

"Well, how the present situation arose is when we first found these [drug testers], we wrote to the sponsors of the investigation, notifying them that they were no longer acceptable investigators. This is picked up in the drug trade news that such and such a person is no longer an acceptable investigator, whereupon the ordinary lay press came down here and wanted full details on the first case. It was very much garbled; and since then we have made a practice of issuing a short press release after the notice has gone to the drug firm."

I asked Goddard if he deplored the fact that his news on blacklisting got into the hands of the press.

"We recognize the reality that it does," he said. "And so

once the letters have had time to reach the sponsors, we simply put out a press release that says the investigations related to this investigator—the sponsoring firms have been notified."

I raised the question of whether Goddard and some of the press had not committed libel.

"We stand to be sued," he said. "Any investigator who thinks he's been treated unfairly has recourse to the courts. He can go and hire a lawyer and get us in court."

I said I thought that in view of Goddard's own "human mistakes" and his getting into the press so much, he'd have understanding, if not sympathy, for Stanley Jacob.

"I have a sympathy with the scentific community in this whole issue," he said. "but we're not talking about actions taken on the publicity. We're talking about actions related to the record keeping, the patient information, the studies that were supposed to be carried out."

I brought up the charge that the number of new drugs in the United States had fallen to an all-time low and that the FDA was responsible.

"I think that's pure baloney," Goddard said. "New drug applications started to decline in 1956 and have been going down ever since." He said that neither the FDA nor the Kefauver Amendments was responsible.

Goddard said that scientific knowledge, on which drug development is based, is cyclical. "I happen to be very confident that within about five years we're going to see the development of a great many more important products than we have today."

A friend had told me he had little hope of overcoming the FDA's formidable barriers to the general availability of two potent immune hormones he had isolated—at least for a long time.

"The question of length of time isn't what we're discussing," Goddard said. "We're talking about whether a product gets on the market or not."

How about making available drugs to relieve pain and cure sickness in people now ill?''

''We're interested in truncating the time too,'' he said, ''but part of that truncation is the responsibility of the investigators. Just what happened in DMSO can slow up the availability of the product to the people in pain, and that's the function of the investigators doing good studies.''

Goddard's tension could be measured in two ways: by the number of cigarettes he smoked—and on this occasion, he sometimes had two burning simultaneously—and by the beat of his fingers on the long conference table. The tape shows that at this point the beat was a fortissimo.

Would Goddard guess as to when DMSO might be marketable if efficacy for scleroderma and a few other conditions were proved—or it turned out to be an effective pain-killer?

''Within six months after the new drug application has been submitted, a judgment will be made by the FDA,'' he said.

That was back in the spring of 1967.

My interview with Goddard left a disquieting sense that many—perhaps most—of the officials' statements were in error.

Goddard reported with a straight face that there was substantial criticism of DMSO at the New York Academy and Vienna symposia. I covered both meetings. His word was hearsay and wrong.

When he complained of the paucity of eye examinations during DMSO treatment, he ignored 310 patients under John and Laudahn, Scherbel's 47, Jacob's and Rosenbaum's 25, D. Hoffmann's 25, A. H. Kutcher's 84, Gordon's 108.

His intimation that a sizable number of patients were under treatment at the Cleveland Clinic was not so. Scherbel had been forced to discontinue his studies.

Scherbel explained the situation in a note to me: "I believe it would be most difficult, if not dangerous, for any clinical investigator to again start studies with DMSO while the FDA remains biased and emotionally prejudiced against the drug." He said, "On the surface, FDA regulations appear acceptable to all concerned. It is readily apparent that large numbers of patients in a special study program cannot be seen at four-week intervals for prolonged or indefinite periods. The expense of laboratory studies as well as the expense of medical personnel make the study prohibitive. Grants are not available because of lack of interest (by drug companies and granting agencies) in these studies."

Scherbel said neither the patients nor the clinic could spare the money; and the families couldn't spend the time to bring the patients in and home again. He pointed out that in the event of abnormal findings (chemical or otherwise)—which would be inevitable—the additional studies demanded by the FDA would prove impossible. Eye examinations required half of a patient's day, and the law prohibited driving with the degree of dilation that would result.

Among the points that struck me as especially noteworthy were Goddard's defense of his police and their methods, his unsmiling reference to the poor, dead "lady in Ireland," his denial of enormous influence over the professions, his exculpation of the FDA in the personal and professional reputations it had destroyed, his rape of the—it must be said willing and consenting—press, and his readiness to put the power of the government against aggrieved citizens in costly and time-consuming litigation, his minimizing of the disastrous trend in drug development and his optimistic prediction that things would soon pick up.

Even Goddard's boast that he grossed $20,000 a year (which ordinarily would mean about $12,000 net) as a small-town busy doctor for a total of fourteen months could be interpreted in many ways.

The week after my Goddard interview and a few months after the FDA had reinstated Dr. Z and given his story a happy ending, I received a note from Dr. Z.

"I am the person who was so badly mauled by the FDA last year," he wrote. "Although there may be no connection, the National Institutes of Health have just disapproved two major grants upon which I was strongly depending." He said he would have to get rid of his research personnel and abandon much of his experimental work on aging, if funds were not forthcoming.

I referred him to the American Cancer Society officer who headed up the research grant section, and I added:

Last week, I had the pleasure of an informal chat with Dr. Goddard. Among the many topics in this candid conversation was the FDA's use of libel to punish some scientists and threats of it to keep others in line.

Your name in particular came up; and I told him then, as I told others at the time of FDA's attack on you, that it is a pity you did not sue him and his agency for libel. You now seem to be reaping the fruits of your timidity.

While Dr. Goddard did not agree with my attitude on this and many other matters, he did say he would welcome the opportunity to go into court to present his defense against the charges. I earnestly hope he has this opportunity.

Dr. Z may have been correct in not suing. He was fifty years old, at the peak of his productive career, and with quite a few obligations to his family. The suit could leave him penniless, in debt and further scandalized.

Dr. Z would stand little chance against officials of the FDA, their own police, the agents of other federal departments, a staff of government attorneys and incalculable resources available at the expense of the taxpayers.

Shortly thereafter, Dr. Z put it this way:

My survival instinct has prevented me from taking a public stand in my own defense. You must appreciate the fact that the FDA has complete power to exterminate me by the simple process of making me ineligible [to do research with experimental drugs].

Their actions can easily lead to my annihilation in the university. The academic community and industry are so completely intimidated that one cannot look for any leadership to counteract some of the punitive actions of the FDA. I find that my name has been permanently blackened in the minds of some persons and some agencies.

I see no way of winning a battle with the FDA, and I

have decided not to be a dead hero, or even a useless one. I am very pessimistic concerning the future status of medical research unless a mood arises to combat overzealous bureaucratic authority.

I am bewildered, resentful, and without too much cheer concerning my future status. Perhaps I prefer the illusion that such things really cannot happen in America and that sooner or later sense and decency will return.

Incidentally, I am usually regarded as a person who has more than average courage. In this case, my policy is surely not the courageous one, but I hope it is the more rational.

Goddard and his associates had promised to send me evidence of DMSO's serious toxicity in humans. At this writing many years later, I still ask the FDA occasionally for the references.

One document, purporting to represent some evidence, was a bibliography of twenty-three scientific papers. I was familiar with most of them, and I searched and was able to dig up all the rest. Not one of them carried any data indicating human toxicity beyond the slight and fleeting odor, occasional transient itching and sensation of heat, a splotch of rash that might last a few hours, or pustules that were gone overnight. When there was any doubt at all, I wrote to the authors. Every single one denied that he had reported or knew of instances of lethal or serious DMSO toxicity in man.

The bibliography sent me by the FDA did include hostile papers—a half-dozen or so. They attacked Jacob mainly for the newspaper accounts and they showed a pretty sour interpretation of DMSO treatment data, or, in some cases, inferior results. Patient improvement or deterioration under treatment often lay in the eyes of the clinical beholder. Improvement in, let us say, one third of arthritic patients could stir enthusiasm in one investigator or bitter criticism in another.

Charles Lebo, M.D., of the University of California Medical Center in San Francisco, it turned out, was the investigator who had induced what Goddard had called a dangerous leukopenia in humans. He did not share Goddard's interpretation, or his "facts" or his alarm.

Lebo's technique called for instilling five drops of 50 per cent or 60 per cent DMSO three times a day into the right ears of convict volunteers for more than two months. Lebo established the complete safety of DMSO when given in this manner. The results suggested that an anesthetic might be mixed with DMSO and instilled into the ear to permit the safe and relatively painless surgical puncture of the eardrum, a procedure which patients otherwise find excruciating. Encouraged by Lebo's and similar experiments, others have utilized this procedure with considerable success.

Lebo's periodic examinations of the subjects—multiple blood counts, complete physicals (including ear, eye, nose, throat, etc.), bacteriology, and blood and fluid chemistry—showed only odor was a side effect, and the convicts did not find it objectionable. As for the leukopenia, Lebo reported that, everything considered, "the validity of this finding is open to question." Since it never before or since has been reproduced, Goddard's reference to it as "intriguing" and "consistent" hardly seems warranted.

The FDA and its spokesmen damned and for many years suppressed DMSO because of its toxicity. What is DMSO's toxicity?

Stanley Jacob, Ed Rosenbaum and perhaps every other expert will agree that any drug can kill any person. If it is given in too high a dose, by an unwise route, in combination with certain other treatments, at the wrong time of a chemical or physical cycle, to an overly sensitive patient or one with organs unable to detoxify it, or to one too young or too old to metabolize it—the drug, any drug, can kill. And perhaps all, or almost all, of the commonly used drugs have contributed to human death at one time or another.

DMSO can kill. But there is no reasonable evidence that it has ever seriously harmed a person. Nevertheless, those who know DMSO best regard it as potentially lethal. It induces a histamine-release reaction occasionally, and if this were severe enough it would send a person into shock. In all the literature I have reviewed and all the authorites I have interviewed, I have not come across a case of DMSO-induced shock.

Animals have been killed with DMSO. They were killed deliberately and with difficulty. A group at the Mason Research Institute in Worcester, Mass., once analyzed the data from their own and fourteen other groups' experiments and found it takes a lot of DMSO to kill mice, rabbits, rats,

guinea pigs, chickens, cats, dogs and monkeys. The drug was given to the animals by mouth, or total immersion to their necks, or by injection into or under the skin, and into the mucous membranes, veins, muscle, bladder, lymph ducts, belly cavity and eye. When enough DMSO was applied to or pumped into the animals for long enough, they became crippled and died. The initial harm in most cases was to the eyes—lens clouding and nearsightedness (not cataracts); next came liver damage and destruction of red blood cells. When rats were immersed up to their necks and sopped up 100 per cent DMSO, all of them died. But when concentrated DMSO was painted on their entire skins daily for as long as three months, the damage was minimal. And when mice and rats were completely immersed up to the ears in DMSO concentrations similar to those painted on the human skin—60 to 70 per cent—all survived repeated treatments.

The Worcester group—Emil R. Smith, Ph.D., Zareh Hadidian, Ph.D., and Marcus M. Mason, D.V.M.,—commented in their article in the September–October 1968 issue of *The Journal of Clinical Pharmacology* that any animal which survived immersion—a thorough dipping—for as long as twenty-four hours would not die of DMSO toxicity. Rats dipped three times a week for six months showed ulcerous dots on the belly and back skin and slight changes in the blood and liver. All effects were reversible.

Dogs and monkeys given whopping doses of DMSO, as much as 3.3 per cent of their body weight applied to their skin every week for six months, showed only one adverse effect—halitosis.

The Smith group established what is called the LD-50, or lethal dose 50 percent, meaning the amount of DMSO necessary to kill one half the test animals. They concluded: "It is readily apparent from these LD-50 values, as indeed it has been apparent from all of the other studies discussed above, that DMSO possesses a very low systemic toxicity."

LD-50 by injections ranged as high as 0.8 per cent of body

weight when given intravenously to mouse, rat, rabbit, dog and monkey. It was two or more times that for intraperitoneal and subcutaneous injection and about three times that—or 2.4 and 2.8 per cent respectively of the mouse and rat body weight when DMSO was taken by mouth. Rabbits, dogs and monkeys were able to take only 1.4, 1.0 and 0.4 per cent of their body weight of DMSO orally to have one half their number survive.

The local damage done by injections depended to considerable extent on the concentration of the DMSO—the higher, the more damage. Here again, in single doses, no matter how much DMSO was given or by what route, if the animal survived twenty-four hours, it was out of the woods—all signs and symptoms of toxicity would disappear, most of them within a week. Among the local symptoms usually seen was the typical inflammatory reaction and irritation of the injected area of the vein; a hemorrhagic, gelatinous and edematous lesion at the site of muscular or subcutaneous injections; local constriction of the vessels, followed by hemorrhage and necrosis, when 100 per cent DMSO was injected intradermally; a transient (three-to-twelve-hour) formation of exudate on injection of 25 percent DMSO into the rat pleura, the sac encasing a lung.

A group from Toulouse, France, headed by Drs. F. M. E. and D. H. Caujolle, reported finding liver damage in animals which succumbed to very high doses of DMSO given orally over a period of days, or intravenously or intraperitoneally in doses amounting to as much as 1 per cent of the animal's weight. When dripped into a vein, or perfused, 50 per cent DMSO was used. "On the basis of these acute and chronic studies, in mice, rats, and dogs," the French group reported, "it appears that the acute toxicity of DMSO is not great; even relatively high doses of DMSO (in 50 per cent strength) are apparently well tolerated. However, these results by no means indicate that DMSO is nontoxic. The chronic toxcity studies, despite the short period during which the drug was

administered, indicate that DMSO does have a toxic potential."

The Caujolle group injected 50 per cent DMSO into chicken eggs after eighteen to twenty-four hours of incubation; and they established the LD-50, and the maximum non-fatal and the minimum always-fatal doses. "From these data," they reported, "it appears that the toxicity of DMSO toward the embryo is low." One in four chicks that survived the LD-50 showed malformation, mostly of the limbs but also of the eye, beak and other structures.

The Caujolles injected DMSO repeatedly into the bellies of newly pregnant mice and rats, and about 7 per cent of them bore offspring with malformed limbs and other defects. When the DMSO was given in low dose but regularly in drinking water to pregnant animals, the baby rats and mice were sound. The mammalian mothers tolerated toxic doses of DMSO well, but the fetuses did show the effects of DMSO—but only when relatively high and repeated doses were given.

Caujolle told me that—contrary to FDA insinuations—his findings did not imply that DMSO might deform human babies. This seems reasonable, because, for one thing, very few women are likely to be injected in the belly with DMSO during pregnancy. At least, not repeatedly. Or anyway, with enormous doses. And, especially, not during the earlier months, when nature's construction of various embryonic organs could be interfered with.

One other animal, the hamster, was sensitive to the teratogenic effects of DMSO.

Don Wood of Portland was among the first to investigate extensively the effects of DMSO on the functioning of organs and the metabolism of laboratory animals.

A quiet, amiable scholar with tremendous patience, Wood administered DMSO in various doses and by several routes and traced it to its ultimate excretion. He made not only an organ by organ check, but he also analyzed what the DMSO

did in different cells and cell structures. He measured its influence in the synthesis, activity and breakdown of compounds in the blood, other fluids and many tissues.

Wood showed that even in the three species susceptible to eye changes under massive does of DMSO, the effects were by no means blinding. Working mainly on rabbits (dogs and swine were the other susceptible species), he discovered that large doses over long periods changed the lens so that the eye became more and more myopic—nearsighted or shortsighted. One group said subtle changes were noticeable in swine after ninety days of 90 per cent DMSO twice daily. Wood and his co-workers effected lens changes in rabbits in two or three weeks by giving them—by mouth and painted on the skin—DMSO doses amounting to 1 per cent of their body weight per day. He emphasized that DMSO does not cause cataracts.

Some reported that, to a degree, the lens changes were reversible, although no one was able to undo the damage completely.

Even ultra-high dosages failed to induce eye changes in other species, most significantly monkeys (only lethal and near-lethal doses induced lens changes).

Mason summed up: "It is of the utmost important to point out that changes in [animal] lenses were consistently seen only when high doses were repeatedly used over an extended period. The routes used to elicit the changes were oral and dermal. It is also noteworthy that in none of the reports on eye changes was there mention of alteration in the visual acuity of the subject. Dogs never showed difficulty in running, jumping, or avoiding obstacles, despite a marked change in lens refraction."

Animal studies showed that if humans reacted as do the average in the most susceptible species, none of them closely related to the human, it might take a pound or two of DMSO a day to do damage. A pound or two of DMSO could last a sick, accident-prone, bruised, arthritic family for months.

The properties which make DMSO unique—especially its ability to dissolve other substances and transport them through the skin and into the bloodstream—pose a theoretical danger. Should a poison or an infectious material (like cyanide or viral DNA or RNA) contaminate DMSO applied to the patient's skin, what would happen? DMSO will inactivate and detoxify some harmful substances; but we will never know which until broad-scale research resumes.

It has been shown that rats injected in the belly with DMSO and given carbon tetrachloride by stomach tube, will suffer awesome liver damage—more than with tetrachloride alone. Few humans can be expected to take carbon tetrachloride by stomach tube while being injected in the belly with DMSO.

Periodically over the years, the FDA has announced that DMSO research will soon resume—or, indeed, that it already is under way. Few centers have the specialists and equipment needed. Consequently, there were very few such studies. When I called this to the attention of FDA officials, they explained, "Well, we can't force doctors to undertake the studies, can we?" Or, "We can't compel pharmaceutical houses to handle DMSO; if they're afraid of a visit from our inspectors, there's nothing we can do about it." Or, always, "We're only enforcing the law."

Looking back on it now—through the rearview mirror—the afternoon of May 19, 1967, may have been a turning point in the careers of Goddard and Jacob.

This was the day when the two men held, as Goddard had proposed it, a "doctor-to-doctor meeting," in the FDA office in Seattle. Jacob, his confidence in Goddard badly shaken after two confrontations with him, still believed the commissioner when he said legal matters would not be discussed but, if he wished, he might bring his attorney to the meeting. Jacob went alone. He was seeking vindication; the alternative could mean lengthy criminal litigation, scandal, professional unfrocking, prison—ruin.

Goddard probably was seeking his own vindication. At stake was the reputation of the FDA as a serious enforcement agency and justification for its police actions. One friendly agent had told Jacob, "It would take a major catastrophe—like a botulinus epidemic—for the FDA to remove any of its men now working on the DMSO matter."

FDA agents had entered many of Crown's warehouses in Camas and smashed bottles of DMSO. One of the Syntex officers, a German refugee, had said FDA operations at Syntex were reminiscent of Nazi Gestapo tactics. A Pfizer officer had been grilled repeatedly by FDA agents; a principal point of interest was: Had there been collusion among the drug houses to hide DMSO toxicity or make unwarranted therapeutic claims?

Rosenbaum said that, so far as he could learn, only scientists who had found clinical value in DMSO had been harassed by the FDA.

Jacob was a problem. When he caught the FDA agents copying his personal correspondence, he had them thrown off the campus. After being muffled at a press conference, Jacob went to the reporters and offered his side of the story. Now he was proclaiming that his rights as a physician superseded the powers of a government agency.

Goddard smiled and stuck out his hand when Jacob came into the Seattle office of the FDA. Jacob described the event in a memorandum to Norm Kobin, his lawyer:

"Dr. Goddard said that he had been wrestling with the question of my 'violations' of the Food and Drug Administration regulations for a long time. He mentioned that he had considered three possible alternatives: 1) to turn the entire matter over to the Justice Department for prosecution—he stated that there were 26 or 27 counts on which this could be done; 2) to send me a letter by the end of the next week, officially blacklisting me; or, 3) to do nothing.

"He said that after careful consideration he had decided to issue a letter blacklisting me as an investigator for new drugs. Then he sat back and waited to see my reaction."

This, Jacob believed, was the cue for the victim to throw in the towel—to cry Uncle—to say blacklisting would be just fine and dandy with him.

Jacob said, "I advised Dr. Goddard that no self-respecting scientist or teacher could allow him to attempt to blacken his name without effective retaliation. I mentioned I would consult with the university administration and with my attorney. I said, 'If you carry out your threat, I will seek redress through the courts.'"

Something had gone wrong. Goddard had offered an amicable solution to a messy problem. Justice was a simple

thing when it involved only a couple of consenting adults.

"Dr. Goddard seemed surprised," Jacob's account continued. "I think he expected me to accept his proposal. He became angry and mentioned that perhaps he had made a mistake, maybe he *should* turn the entire matter over the Department of Justice. I told him if this was what he wanted to do, he should go ahead.

"Dr. Goddard said he thought I wanted to become a martyr."

Jacob said that at this point he and Goddard went into a discussion of the merits of DMSO.

"Dr. Goddard does not know the literature on this drug," Jacob reported. "He had only superficial knowledge of what has been done. . . . I told this to Dr. Goddard; and I pointed out that, contrary to Dr. Hodges' statement that no drug company had submitted a formal request to release DMSO as a prescription item, three companies had done so—Merck, Syntex and Squibb.

"Since we did not seem to be making any progress," Jacob said, "the meeting came to an end. We shook hands."

Goddard told Jacob that he would receive an official statement blacklisting him by the twenty-sixth of May. It never came to pass.

Dr. Richard Brobyn, a smart young physician and general surgeon of Maple Grove, Pennsylvania, had worked out a bold plan to test DMSO's safety. As a consultant to Merck, he devised two regimens to be tested on volunteers—a short-term protocol covering two weeks, and a long one which would go on for three months.

Under this plan, the subjects would be given ten times the permissible dose of DMSO. Every single day, for two weeks. And if there were no serious effects from that, for three months.

When the FDA stopped virtually all experiments with

DMSO, Merck lost its interest in DMSO and further human tests. But not Brobyn. He persisted. He presented his plan to Squibb and got them interested.

Squibb proposed that the FDA join them as partners in the venture. They would share the costs. The FDA agreed.

After two years of repeated promises to permit DMSO to be tested "properly," of contending the drug had shown severe toxic effects but refusing in each case to offer specific references, of saying doctors were still treating patients experimentally but declining to say where or who or on whom, of insisting that adequately equipped physicians could resume treating their patients but refusing to admit publicly that producers and distributors of DMSO were reluctant to accept the FDA's terms—after all this, the FDA finally gave Squibb and Brobyn permission for a controlled test of the drug for safety.

One October evening in 1967, a group of sixty-seven healthy male prisoners at the California Medical Facility in Vacaville lined up in a large chilly hallway. They stripped, hung their clothes over chairs, and covered themselves from head to toe with a colorless gel—DMSO. Another thirty-three volunteers stripped but were untreated, because they were controls.

After two weeks of regular plasterings with DMSO, the procedures were stopped. The extensive examinations—including spinal taps, bone marrow punctures, eye studies, EKG for heart function, EEG for brain performance, and numerous tests of the blood, urine and other body fluids—were made again for the last time.

Examining physicians declared that the drug trials had been satisfactory; no prisoner-volunteer had shown evidence of a serious toxic effect of the drug. The ninety-day trials began.

The second group, of sixty experimental subjects and twenty controls, represented what the examining physicians described as "the largest and most competent toxicological

study ever undertaken." The test subjects received ten times the ordinary therapeutic dose day in and day out; they were inspected and otherwise tested regularly—and so were the control subjects. Each man was paid $300 for his part in this study.

During the first three or four weeks, about twenty experimental subjects and a few of the controls dropped out. They had several reasons: 1) They didn't like the body odor DMSO induced or, in some cases, skin reactions; 2) they were not being rewarded enough; or 3) they went free or were moved to other prisons. On the other hand, several continued the test despite transient headaches and repeated skin reactions.

When the three months were over, Dr. Brobyn and his ophthalmologist partner, Dr. Frank Hull of Fairfield, California, filed an abstract on their findings. It said in part:

"This study plus monkey data at up to one hundred times the therapeutic dose for over a year have shown that the lens change is species specific and does not occur in primates. [Man, monkeys, apes and lemurs are primates.] Future areas of study based on the premise that DMSO is an extremely safe drug are listed."

Dr. Brobyn told me, "Of course, DMSO is a safe drug. I don't think there's any doubt about it. It did exactly what we intended . . . right to the letter."

Dr. Hull, the ophthalmologist, said there was no eye toxicity. Or, for that matter, no other serious side effects either. Don Wood, who had reported DMSO's effects on rabbit eyes, agreed that the human subjects showed no impairment.

The side effects were the same as those reported during the past five years by hundreds of doctors. Oyster odor of the skin and a garlic halitosis were common. The skin irritation was not rare, but most of those who experienced it went right on taking their DMSO. Headaches occasionally came and went. At ten times the ordinary dose, DMSO was amazingly gentle.

There were a few unexpected dividends. One man reported that his chronic back pain, which had required the removal of two spinal discs, had decreased. Another, whose ankle had been painfully stiff since a 1961 automobile accident, felt relief. Some said their postnasal drip and sinus conditions were better or their bursitis disappeared. The tests were for safety, however, not efficacy.

The Vacaville tests vindicated DMSO as no other drug in all history had been vindicated of all suspicion of immediate toxic effects.

Hull and Brobyn examined the subjects for many months after the end of the study—Brobyn flew from Pennsylvania to California fourteen times that year. FDA investigation dropped in three times during the course of the study; and Stanley Jacob and one or two other investigators stopped by occasionally to chat with Hull, Brobyn and some of the prisoners.

The study cost $90,000, and this was split between the FDA and Squibb. It probably could be described as a classic in toxicology.

While the experiments gave DMSO a clean bill of health, so far as safety was concerned, nothing really came of them.

At 12:50 P.M., February 5, 1968, E. Rottenberg of the Ozothine Laboratories, Hauts-de-Seine, France, applied for a patent for DMSO "for treatment of all irritating conditions of the alimentary canal."

"By irritating conditions of the alimentary canal," the applications stated, "one understands as included gastritis, duodenitis and colitis, acute and chronic, of all origins and all types, accompanied or not by ulcers."

Rottenberg's prescriptions was 4 per cent DMSO three times a day—or the equivalent of three times 60 mg of 100 per cent DMSO—taken orally as syrup, drops, tablets or another form.

He cited as support for his application these examples:

ACUTE GASTRITIS—Twenty-eight patients unable to work went back to their labors following five to eight days of treatment, rid of such symptoms as nausea, vomiting, pain, gastric heaviness; their stomach secretions became normal and so did their general condition. One year later, twenty-one were still free of symptoms, working and off their diets. During this time about ten had undergone treatment again for about fifteen days.

CHRONIC GASTRITIS—Thirteen patients on assorted treatments all relapsed on stopping treatment. On DMSO by mouth for one to two months, symptoms cleared up and all of them went back to work. At the end of a year, all of them remained improved, although some had resumed treatment two or three times.

PEPTIC ULCER—Five patients were completely cured of recent peptic ulcers with oral DMSO, without recurrence during the following year.

ENTERO-COLITIS—Six patients with abdominal pain for several months and with diarrhea, emaciated and asthenic, began to improve after eight days on oral DMSO, and all were back at work in two months, pain-free and in good shape.

MUCOMEMBRANOUS COLITIS—Three patients were "cured" after three weeks of oral DMSO.

When the DMSO is combined with star anise, the appetite improves, the application stated.

At this time, nothing had been heard from the U.S. Patent Office about the patents applied for six years earlier in Jacob's and Herschler's names for the state of Oregon and Crown Zellerbach.

Professional and public opinion began to close in on Goddard and the FDA. One committee within the FDA and another outside it were gathering information on the agency. A growing number of doctors were defying Goddard and the laws he professed to enforce. As professional rebellion grew,

bureaucratic strictures relaxed. The FDA once again seemed to be on recidivous course back to its familiar state of futility and apathy.

Twenty-eight months after taking the job, Goddard resigned as FDA commissioner. He cited "personal reasons" to HEW Secretary Wilbur J. Cohen as the cause of his departure; and Cohen, in accepting the resignation, paid him the compliments usually awarded a public servant who quits under non-scandalous circumstances. Some speculated that the Johnson administration couldn't take any more of Goddard's "activist" behavior in an election year; some said he was physically and emotionally tired of the binds he found himself in, many of them of his own creation. Others said that he was being passed over for promotion. In any event, he was picking up his fat federal pension and retiring to the vice-presidency of EDP Technology, Inc., based in his wife's old hometown, Atlanta, Georgia.

In his swan song—an address before the AMA's American College of Legal Medicine in San Francisco, June 16, 1968—he defended his finding several clinical investigators ineligible and stated that "this kind of surveillance continues"; he said that the finding of "less than a dozen investigators who have raised suspicions" ought not to loosen confidence in the ability of clinicians generally as investigators "given proper orientation and guidance."

"The rascals will be exposed," he said, "even though their signboards may remain untouched over their office doors for periods longer than we can tolerate." He castigated the lawyers in his audiences for inadequately defending the nation's poor; and he charged the nation's doctors with failing all classes. He denied categorically charges that his administration was leading to "therapeutic nihilism" ("Professional nihilism comes through as the message," he said), or that the FDA had imposed censorship on the medical profession. And as for the package insert, he insisted that it should not be viewed as a mandate from the FDA's "non-

expert in-group or as the dogma of the drug therapy," but rather as the result of a thirty-year-old law requiring directions for drug use and "an aid to physicians who want to know how to use the drug it has accompanied, and it is the only FDA-approved public record of what we know about the safety and efficacy of the drug."

Goddard also defended his crusade for a Drug Compendium, the mock-up of which was big city telephone book size. A critic, Dr. Louis Lasagna, had said one version of it sounded like "a modern five-foot shelf of package inserts," and he expressed apprehension that such a volume would curtail the doctor's practice of good medicine.

Goddard's valedictory could be interpreted as a bitter denunication of men who had challenged his bid for power over the practice of medicine and who had helped put him down in defeat.

Part Three

Goddard's successor as commissioner was Herbert L. Ley, Jr., M.D.

Ley was graduated, cum laude, from Harvard Medical School in 1946 and became Chairman of the Department of Microbiology in the Harvard School of Public Health. He had done stints on the faculty of George Washington University School of Medicine and in the sciences branch of the Army, before taking a job with the FDA at age forty-four. He was a large man, industrious, approachable, and, in a preoccupied, professional way, amiable.

I talked with Ley on the afternoon of St. Valentine's Day 1969, in his office—Goddard's old headquarters. J. Kenneth Kirk, the Associate Commissioner of Compliance, sat in.

From the outset, Ley made it clear that his conduct of the office would differ from Goddard's. He said, "Dr. Goddard is one unique type person; he had done many things that it would be difficult for me to do as an individual. I'm another personality type. I am less flamboyant than Dr. Goddard. I think that there may be some things I can do perhaps better in my way than he could do. I am strongly committed personally to a full, fair but firm enforcement of the statutes which guide us as a nation."

My principal mission was to nail down, if possible, any evidence of severe DMSO toxicity. Reasonable proof that DMSO had killed or seriously harmed people would tend to justify the agency's extreme delay in releasing the drug.

I asked Ley if he shared Goddard's assumption that DMSO was highly toxic.

The commissioner was given to answering some questions with small speeches which were not entirely responsive. In due course, he came to this part: "There are possibilities of various types of hypersensitivity reactions, some of which have been documented in the literature, which may be quite severe, leading to death in a few people—"

I interrupted here: "Do you recall where this was reported, Doctor?"

He answered: "The reports are in our files here, and I do not have this information at our fingertips. But in review of the whole file a year ago, the hypersensitivity type of reaction is a rare one with DMSO. But it obviously does occur."

This was the sort of thing that Jacob, Rosenbaum, Brobyn, Wood, Scherbel, Brown and all who were most familiar with DMSO feared and, in a way, expected, an allergic reaction, with the collapse of blood vessels, chaotic spasms of the pulmonary and digestive systems, convulsions, and, very often, sudden death. It was what they feared, but what had never come to pass. The massive and still mounting medical literature on DMSO showed no reaction stronger than a mild and fleeting histamine release syndrome. The drug seemed to have a clean slate after millions of DMSO treatments.

"You say there have been several deaths due to hypersensitivity reactions to DMSO?" I asked. I had to be sure.

"This is apparently the case," Ley said. He said the evidence was incorporated in a "white paper" prepared a year earlier, and he promised me a copy soon. I hoped it would more specific and informative than the "white papers" I had seen. He, and Kirk as well, had no idea how many patients were under experimental treatment with DMSO.

I mentioned the apprehension incited by FDA agents' "visits."

"We have had no reason to pursue this type of approach

within the past year," Ley said. "There's been no stimulus for it."

Ley and Kirk both denied vigorously that the FDA had blacklisted scientists. Ley described in several hundred words precisely what had been done to scientists, and the actions he described met, in every detail, what I would consider the dictionary definition of blacklisting.

I asked whether Ley had changed the procedure, and he answered, "We changed it by adding the second level of review."

When I brought up the damage done by this type of character assassination, it occurred to Ley that we were running out of the time allotted to me. Both men suggested that if I had further questions and would write them out and mail them in, they'd be glad to answer them.

I left the Ley interview, as I had the Goddard interview, perplexed that these high officials seemed so lacking in solid information about the most spectacular and the most controversial drug of our time and, as Congressman Wyatt had expressed it, a "persecuted drug."

Not only did the FDA lack data to support its charge that DMSO was forbiddingly toxic but it was proving amazingly uninformed on the results of laboratory and clinical studies. At this time, the proceedings of the New York Academy and the Vienna meetings had been published and many papers were being republished in various jounals. There also was a strong surge of scientific reports, mainly from abroad, flatly suggesting that DMSO was indeed a "wonder drug," and one without great toxicity.

The Food and Drug Administration officials answered questions about DMSO with short stereotyped notes and one of two enclosures—a so-called "white paper" or a "fact sheet."

The "white paper," which ran variously between two and ten thousand words, may well become a museum piece in governmental communications. There is no signature to identify the author and no letterhead to indicate its FDA origins. It has never been presented before scientific or medical audiences. There are no data, no bibliography, no references, no author or agency with whom to check the statements of "fact."

The second type of enclosure, a "fact sheet," is presented under the FDA letterhead. It is a digest of the "white paper," with interchangeable phraseology, and is equally anonymous, data-less, without references or identifiable or responsible sources. Scientists have disputed the innuendo, insinuations and many of the alleged facts in the "white paper" and the "fact sheet." Here is a version I have boiled down from the latest, most moderate, and most honest "white paper":

> Interest in possible drug uses for DMSO in man accelerated rapidly from 1962 to 1965. In October, 1963, the first Notice of Claimed Investigational Exemption for a New Drug (IND) to provide for clinical testing of DMSO in

humans was submitted. Also submitted were 3 New Drug Applications (NDA's) for commercial marketing of DMSO for drug use.

Preclinical Evaluation for Safety

Data from preclinical animal studies in the first investigation filed with the FDA failed to support the safety of DMSO for all the proposed clinical trials. The FDA recommended restricting the product to a very limited cutaneous study.

The data disclosed serious toxic signs in some animals, appearing at dose levels which suggested little or no margin of safety in humans. However, in other species the toxic manifestations appeared only at high dose levels. Some of the more serious adverse effects reported were hemolytic anemia, lesions of the gastrointestinal tract, liver, lung, and spleen; dilatation of nerve sheaths of brain and spinal cord; hematuria, abortions and teratogenic effects. In all animals corneal and lenticular changes of the eye were observed. These eye changes were more moderate and marginal in the monkey.

Concurrently, the results of DMSO testing in humans were evaluated. However, before a scientific opinion was reached, articles appeared in the popular press, representing DMSO as a "'wonder" drug, for treatment of a variety of diseases. There were no adequate scientific data to justify these glowing accounts, but the publicity excited the interest of the medical profession and the laity. DMSO was readily available in many communities in commercial grades for industrial use and thus there was an easy and unrestricted source of supply.

An estimated more than 100,000 patients received DMSO during 1964 and 1965. Many of the clinical studies were poorly designed and conducted, but claims of excellence were made on such uncontrolled studies.

The adverse effects of DMSO on the eyes of animals

were manifested as change in the refractive index of the lens and by nuclear sclerosis. These adverse reactions were not disclosed to the FDA by responsible sponsors until November of 1965.

Reported cutaneous application of DMSO has disclosed a spectrum of allergic-like reactions, from generalized urticaria and respiratory distress to angioneurotic edema and anaphylaxis. Adverse experience involving the human eye are described by such phrases as "impaired vision of rather vague type," "decreasing vision," bleary vision," "like wearing dark glasses," "vitreous opacity," "pain in one eye," "double vision," and "increased relucency."

Clinical testing was discontinued by voluntary agreement of all the sponsoring pharmaceutical firms and the FDA because of the question of safety.

On November 25, 1965, the FDA announced termination of clinical testing and investigational use of the drug, except in laboratory animals. Clinical testing with DMSO was not completely prohibited but, in the interest of patient safety, was strictly controlled.

During 1966 a comprehensive evaluation of all available data on DMSO indicated that further clinical investigation of the drug was justified for cutaneous application in serious conditions, such as scleroderma, persistent herpes zoster, and severe rheumatoid arthritis, for which no satisfactory therapy was available.

Between October 23 and November 6, 1967, a [14-day toxicity] study disclosed that, for treatment of relatively benign conditions, DMSO was reasonably safe; ophthalmological examinations were not necessary when cutaneous use of the drug was limited to 14 days. In the second phase, a 90-day study, adverse reactions were headache, pruritus, neausea, sedation, and dizziness. Examinations disclosed no demonstrable eye changes, but a small percent of subjects complained of hazy vision and burning

sensation in the eye. In both phases of the study there was a tendency toward eosinophilia (histamine-type of response) and skin irritation during treatment.

DMSO appears to give temporary symptomatic relief in some patients with scleroderma. In our judgment the adverse reactions reports received do not appear to seriously jeopardize safety.

A government agency is the sponsor of a notice for use of DMSO as an endocellular cryophylactic agent in the process of freeze preservation of blood platelets for the infusion of blood elements into thrombocytopenic, leukopenic and aplastic anemia patients. These studies are being carried out in 5 medical centers under the government agency and at present approximately 100 patients are receiving such treatment. In addition, there are two independent clinical investigators conducting similar studies in other centers.

At present 21 sponsors of IND's are conducting clinical tests on a total of approximately 2404 patients in the treatment of acute and chronic conditions.

The "white paper" could have been the source for ever so many doctors. When the subject of DMSO came up, some doctors were likely to say with conviction, "DMSO? Very toxic, you know. Could blind a person. Hard on the liver too."

From this point, the dialogue usually went:

Q: Ever given DMSO to a patient?

A: No—can't say that I have.

Q: Ever use it yourself?

A: Never.

Q: Ever know anyone who was harmed by it?

A: No.

Q: Then how do you know it's risky?

A: It's right there in the literature. The FDA says so.

Many patients sent Stanley Jacob letters and accounts showing how their physicians had discouraged the use of DMSO, often on information from the FDA.

There was an exchange between Dr. Y and a labor union official. Dr. Y wrote: "The initial claims of success have not been substantiated by further investigation, and it is currently being used on a research basis only . . . most of the reports seem to indicate that it does have some value in acute muscular strains and sprains when applied to the skin . . . however it does have some side effects causing dehydration and loss of fat in the skin with dryness and flaking because of its powerful solvent action."

He then added: "As to the charge that the FDA is dragging its feet in approving it for general use, this does not appear justified to me. In some respects this situation is analagous to Krebiozen, the anti-cancer drug that had great claims made for its success but were not substantiated when placed in the hands of competent investigators. I have taken the liberty of checking with others who would be more knowledgeable in this field and they seem to concur in this evaluation."

Dr. Y made it clear—as so many critics of DMSO had before him—that "I have had no personal experience with it."

L.A. Healey, M.D., a director of the Arthritis Foundation of Western Washington, wrote in an article that he had tested DMSO, before the FDA ban, on patients with rheumatoid arthritis.

Healey wrote, in part:

> It was supposed to relieve pain and stiffness in joints and tendons, not only in acute inflammatory conditions like bursitis or sprains which are self-limiting and will in time clear up by themselves, but in chronic diseases such as rheumatoid arthritis as well. As is well known, there is no complete cure for rheumatoid arthiritis and anything

which seems to show promise naturally arouses great interest.

There was some evidence of cataracts developing in animals given DMSO experimentally.

Before it was withdrawn, I had the opportunity to try DMSO in patients with rheumatoid arthritis. I am sure it was not as good as was claimed. It gave temporary relief of joint pain but did not affect the swelling or joint inflammation. . . . I do not belittle this, as temporary relief is frequently welcome, but it was no cure for arthritis and did not appear to alter the disease process in the joints.

Healey complained that "headline writing, of course, is a separate art; closer related to the carnival barker at times than to the story itself."

The headline on Healey's handout was: "DMSO—ANOTHER 'MIRACLE' DRUG EVERYONE SHOULD AVOID NOW."

The spirit of the FDA reached beyond America's shores. It was felt keenly in Germany, where science, medicine, and the pharmaceutical industry had come to reject the FDA. The trouble was, the FDA continued to sound its alarm through "white papers," "fact sheets" and the like, and no one dared openly dispute it. As a prescription drug, DMSO was sold with multiple restrictions as to dosage and administration routes; and the industry decided not to promote it. No drug can succeed without promotion.

Late in 1968, I wrote to Priv. Doz. Dr. med. Gerhard Laudahn, Director of Shering AG, in Berlin and asked how Germany was responding to the availability of DMSO.

"Much to my regret," he replied, "DMSO sales have not come up to my expectations.

"There is still the psychological handicap that soon after its introduction onto the market, DMSO had to be withdrawn and then was re-introduced more than a year later. Hence,

there is still an attitude of reserve, and the preparation is still being very carefully observed."

Laudahn was satisfied with DMSO's performance as a drug.

"The expectations we placed in DMSO regarding its use in acute inflammatory conditions of the musculoskeletal system have been fully realized," he said. "As regards chronic conditions, such as rhematic arthritis, scleroderma, etc., we have not come across any more information, since in Germany and Austria the use of DMSO is limited to 14 days."

He said that DMSO research in Germany had stagnated since "the severe set-back in the U.S.A.," meaning the FDA crackdown. He said that in Germany and the United States, "it may be that DMSO will not regain its original popularity unless completely new fields of application, such as cancer, for example, are opened."

I was not the only one who had difficulty getting solid information from the FDA. Paul de Haen of New York was having his troubles too.

A highly respected authority on the introduction of new drugs—or old drugs in new guises or new combinations—de Haen interprets developments for the pharmaceutical industry and others concerned with the drug trade throughout the world.

Near the end of February 1969, he told me that he had found it impossible to get essential statistics from the FDA.

He said the FDA did not differentiate between new drugs, single drugs, combination drugs that are newly marketed, and drug applications for variations of them, or for new uses for old drugs.

"You really never know what they have," he said.

The British, on the other hand, leveled. They gave honest figures.

In his annual review, *New Products Parade 1968*, de Haen reported that during the decade 1959–68, in the United

States the total number of new drugs had declined from 315 (in 1959) to 87 (in 1968), the number of new single chemicals from 63 to 11, duplicate single products from 49 to 26, combination products from 203 to 50, and new dosage forms from 104 to 21.

In 1968, a majority of the new products introduced into the United States came from abroad; only three of the seven new original products, and one of the four other derivatives of old compounds were American. It was apparent too that researchers were publishing more and more about less and less—perhaps a progressive approach to the end point of writing everything about nothing. De Haen said he had harvested 5,780 reports on pharmaceutical specialties in 1968 as compared with 4,969 during the previous year.

Bad as 1968 had been, it was still much better than 1969. During the twelve months, the total number of new products dropped from 87 to 62; and the number of new single chemicals introduced in the United States declined from 11 to 9, with comparable cuts in other drug categories as well.

Despite its scientific decay, the drug industry prospered. Americans were buying more drugs (old ones, that is) than ever before, and the drug houses' profits were achieving new records each year. A pill-hungry society would buy whatever was offered.

"Quadriplegia is the saddest thing that happens to people," Jacob said. "It occurs most often to the young and healthy—to soldiers fighting our wars, to youngsters driving, to athletes in personal contact games.

"As a quadriplegic, you lie in bed, a total vegetable, unable to move any of your extremities. Your mind functions, but you can't pass urine. You can't have a bowel movement without help. You are totally dependent upon someone else to perform the basic functions—to keep you alive."

I had asked who stood to gain most from DMSO.

"As I get to know the quadriplegics, ever so many of them eventually will say to me, 'You know, Dr. Jacob, I couldn't even commit suicide.'"

At this time, he was treating eight quadriplegics; and of them only one had presented a recently incurred injury. He felt, as do most doctors, that treatment is more fruitful in new than old conditions. The one fresh case was that of a sixteen-year-old girl, a fine athlete, who dove off a board and landed on her neck on the bottom of the pool.

"Her doctor was pessimistic but willing to try almost anything that offered a glimmer of hope. She was a complete quadriplegic—utterly helpless.

"She was on DMSO for an entire year. Gradually—one by one, it seemed—her organs began to function again. Eventu-

ally she walked. And now she is in college, doing very well."

It was 3:30 P.M. on Saturday, April 5, 1963. Grey Keinsley, eighteen, was driving from Greeley, where he was a freshman at the University of Northern Colorado, to Denver, where he was going to apply for a summer job with the State Highway Department. The Rocky Mountain sunshine and bracing air flooded through the open suntop of his VW, and it might have been that open top that saved his life. To this day he doesn't know what happened.

They lifted the athletic body off the barbwire fence where it had been hanging, limp and battered, and they took him, still breathing but unconscious, to the Community Hospital at Longmount. The doctor said, "Have this boy's family get here without delay."

The way it looked to the doctors: the numerous bruises and cuts would heal in time—if there was time. One could survive the concussion. But the broken neck was another thing; x-rays showed a fracture four over five, a spinal cord block between the cervical vertebrae four and five, a vital link in communications between the brain and the body below the neck.

When Grey heard his parents' voices, he came out of the coma momentarily, but he was delirious for weeks.

Mrs. Dorothy M. Keinsley of Littleton, Colorado, had told me of Grey's struggle. His father being in the U.S. Army, Grey had lived around the world. In the United States, he had been a babysitter, grocery sacker, carry-out boy, delivery boy for newspapers and heavy appliances, hamburger cook, yard worker, snow shoveler, car washer. He had attended schools in Japan; and at the American High School in Poitiers, France, for three years he had played on the football team. He had been an Eagle Scout and junior scout master. He said his religion was "workable."

Grey liked girls and they liked him; he was a good student; he played trombone in the high school band, danced well, sang well, knew what to do about a sick car, was six-feet-one physically. He said, after his catastrophic accident: "Mom, the best part of me is intact—my mind."

Grey was admitted to Fitzsimmons General Hospital in Denver—a fringe benefit for army families—and he stayed there for six and a half months. When they transferred him to Craig Rehabilitation Hospital in West Denver, he could make only shoulder motions and flail his arms. They fitted him with carbon dioxide-powered braces on both hands, and he was able to come home for Christmas 1963.

One day the neurosurgeon said he'd talk with Dorothy. "The neurosurgeon told me that henceforth Grey's only motion would be to move his head from side to side and grin," Mrs. Keinsley said. "If this was true, I knew Grey's life-span would be very short. But I didn't believe it."

A few weeks later, the neurosurgeon gave it to Grey—straight. Grey listened attentively and thought a minute; then he said to the doctor, "One day I will swing my legs off my bed and I will offer to bet you I am going to walk. At that time, put your money where your mouth is now."

Mrs. Keinsley saw it this way: "We have not had adequate finances to be classified as affluent, but we've had twenty years of training in frugality, and this made me astute in managing." The Keinsley mother and son got help from several sources; but all of them together didn't quite pay the medical bills.

Mother and son did draw heavily on one resource. Dorothy said, "Grey loves all life and the world. His pantheistic approach has served as a buffer against the cruelty of the world and the cruelty of man to man when adversity strikes.

"I have a strong faith that God will never give one a bigger burden than one can carry, although there have been times when I thought He punched my card twice."

Grey read Ann Sullivan's article about DMSO in *Pageant*

magazine. The part about the rejuvenation of plants made him wonder: "If DMSO will do this for useless limbs on trees, what would it do for useless human limbs?" He wrote to Jacob, and his physician made the tests Jacob had required. On February 13, 1965, Jacob came to the Littleton home of the Keinsleys and swabbed Grey's neck with DMSO.

"The most dramatic change happened that first day," Dorothy told me. "Grey had had a constant pain in his right shoulder from the time of the accident, and he had learned to live with it. Late that day, Grey discovered the pain had gone. He was almost incredulous. He expected the pain to return, but it never has.

"Other improvements were gradual, as Dr. Jacob had predicted they would be. One of the welcome changes was in his thermostat; until DMSO, it fluctauted between excessive heat and cold. His body temperature became normal."

Neurosurgeons and nuerologists will say that there is some spontaneous return of function for the traumatic paraplegic—but only in the first two years following the injury. If significant improvement doesn't occur within that time, it never will. There seemed to be no documented case to the contrary.

That principle is passé.

These are some of the battles as Dorothy recorded them, in Grey's war:

4/5/63 The accident. Grey was expected to die. He lived in a respirator.

2/5/64 Leaves Craig Hospital and starts classes at U. of Colorado, Denver Center.

2/13/65 Starts DMSO treatments. Shoulder pain stops.

5/1/65 Temperature sensation stabilizes.

6/1/65 Healthy color replaces pallor. Grey feels fine and smells terrible (from DMSO). He no longer is constantly tired.

Return of major functions of the body:

8/22/65 Lifted both arms over head and put on T-shirt without help.
9/12/65 Pains in left hand and wrist. First since accident.
10/17/65 Sensation to touch on right side of body starting to move below nipple line (2 to 23 inches).
10/29/65 Severe pains in right hip.
11/1/65 Sharp pains in upper left arm for several hours.
11/9/65 Severe pains in right hand and arm.

FDA banned use of DMSO

Pains subsided in a few weeks but he did not lose any of the improvements.
11/6/67 Stops wearing body brace (similar to corset to support lower back).

8/22/68 *Resumes DMSO.*

9/6/68 Tingling sensation deep inside neck in area of lesion.
10/7/69 Pains start again in left hand.
10/9/68 Feels heat in right hand from coffee cup—first time.
11/16/68 Moves right leg—feebly.
12/11/68 Exerts pressure shaking hands with right hand.
12/31/68 Sensation to touch on entire right side of body. It is spotty and not too clear.
1/19/69 Exerts very weak pressure with left hand.
3/5/69 Moves right thumb.
4/1/69 Raises right leg in bed.
4/13/69 He lifts his body slightly off the bed or wheelchair by using his arms locked at the elbows.
6/6/69 Grey receives his Bachelor of Arts degree in economics.

6/17/69 He moves toes on both feet—weakly thru 8/12/69
10/12/69 Moves left leg—feebly.
1/1/70 He writes by hand legibly and at length.
8/17/71 Grey received his master's degree and began looking for a job, preferably in a bank.

The chronology omits mention of the many people and organizations who lent help of various sorts: The Mayfield Foundation, which supplied a hydraulic hoist (so his mother could lift him into the family car) and an electric typewriter, cab drivers who gave him a lift until the state transportation to and from school, and student grants for his tuition.

The people most responsible for Grey's victory were his mother and his sister, Pamela. Pamela worked while attending school, helped her mother a great deal with household and nursing chores.

Mrs. Keinsley had to get up at five every morning and spend two hours preparing Grey for school; he required a catheter or condom to void, and even with the hydraulic lift, getting Grey into the car and into school was an arduous job. At first, Dorothy attended classes with him and made notes for him.

Grey supplemented the meager family income—from welfare, child support, and Pam's baby-sitting jobs—by grading papers and tutoring students; this brought in a cool twenty-five or thirty dollars a month; he dictated his comments and grades to his mother, who, necessarily, was his almost constant companion.

When Grey first proposed writing to Jacob, Dorothy hesitated. She was afraid that if Jacob rejected the idea, it would crush her son. She had earlier received three flat and emphatic medical opinions that her son would be completely helpless for all his days. She asked Grey: Could he take it if Dr. Jacob was negative? They sent off the letter to Portland.

In insisting that her son would find help, Dorothy Keinsley

did not delight all the doctors. "One doctor bellowed at me like a bull moose in rutting season," she said. "Don't you know your son is paralyzed?" He screamed. I explained that no one knew it as well as I."

Mrs. Keinsley said that Jacob not only did not charge for his services, but, out of his own pocket, paid the bills for the exhaustive medical examinations, which were done locally. Jacob makes a house call at the Keinsleys' whenever he is in Colorado.

When three years of supplication by himself and many others had brought no sign of relenting from the FDA, Jacob decided to resume treatments anyway. He told Grey he thought that injections into the back of the neck, in the vicinity of the scarred spinal cord, might speed up recovery; he asked if Grey was willing to accept the considerable pain of the injections and the increased odor from them. Grey agreed, but first he wanted to square it with others. He talked with his professors at the university, saying he was willing to drop out of school to save other students from the aroma. One professor said, "Grey, I want you to attend classes as usual. If worse comes to worst, there will be two people present in your classes—you and I."

The students, every single one of them, stuck with Grey, rooted for him, helped him however they could.

"In the three years that DMSO was denied him," Mrs. Keinsley said, "Grey did not progress, but neither did he lose any of the ground he had gained.

"I wish I could tell you that Grey arose from his wheelchair under his own power. This is coming. We are working toward that goal not only for Grey but for all people who are paralyzed by spinal injuries."

A specialist in orthopedic surgery and fractures has drawn up a series of exquisitely detailed reports on the nerve-by-nerve and muscle-by-muscle comeback of the patient. They probably are without parallel in medical annals.

Among the most obscene terms in medical science are—and you should excuse the expressions—"subjective," "testimonial" and "clinical impression." They rank with "uncontrolled studies" as fit only—if at all—for back fences. In medicinemanship, the purist physician can put down the doctor who says his patient had improved or been cured, with, "Sorry, Doctor, I can't credit testimonial claims." Or, "Doctor, do you have any other clinical impressions?" Or, "I assume this was a double-blind controlled study," or, if it was a double-blind, "I must say I question the adequacy of your controls."

The layman, of course, doesn't stand a chance. The physician can dismiss all the data and all the facts and end any discussion with a single question: "Sir, are you a doctor?"

One man who had been almost blind in one eye for many years told me he had made great progress with DMSO. Moreover, he demonstrated this by walking unaided in public areas and describing objects and events. His good eye was covered.

"How much credit can I put in Joe's story?" I asked the ophthalmologist.

"Not too much," he said. "Joe is looking for miracles. There's no improvement, actually. We can measure it."

"Then he really doesn't see color with has bad eye, as he claims?"

"Well, that's subjective," the doctor said. "You can't measure that objectively."

Prior to treatment with DMSO, Joe could distinguish only light and dark—not form or color. Now the man had identified for me size, shape, form, color; he could describe motion and action in considerable detail.

"I know," the eye doctor said. "I've talked to the physician who's been treating him with DMSO. But I haven't been able to check a thing so far that's changed."

Joe said, "Well, he's the doctor. But it's my vision."

And the physician who had treated him, Stanley Jacob, said, "Joe's right. I've tested it; his vision has improved."

Other blind patients have been chided by their ophthalmogists. A midwest woman wrote:

Dear Dr. Jacob:

Dad's ophthalmologist refused to acknowledge Dad's eye condition. He said there was no improvement.

Now for the facts: Dad walked from his house to the bus-line 2½ blocks, caught the bus, walked a block from the bus to the doctor's office. After the exam, he walked eight blocks to shop for a suit, then another three blocks to a shop that had recently moved—Dad had no trouble finding it or finding his way home. Dr. A.B.C. says, "Dad is such a determined man." Nuts! Dad can see.

A year ago when he started on DMSO, Dad was completely dependent on his wife, neighbors and my husband and me to take him to the store or bank, to cut his meat, to do everything. Now he takes care of all his affairs, watches TV, and is immaculate. A year ago he was messy and a constant worry to all of us.

Physicians usually say their killjoy attitudes "save the patient from false hope." Their practices often shatter all hope—true or false.

The conservative majority of doctors contend that the answer to moot clinical questions is controlled studies. They feel that these experiments—especially those of a double-blind nature in which neither the patient nor the physician knows who is getting the test drug and who the placebo—will determine whether a drug is safe and efficacious.

FDA officials complained that the big trouble with DMSO lay in the lack of controlled studies. Some said all evidence had been "testimonial-type."

Actually, there have been many controlled studies with DMSO. They were conducted by well-regarded physicians, sanctioned by the FDA and run under the most rigid regulations ever proposed for a candidate drug.

In fact, it would be difficult—if not impossible—to name a medicine which has been subjected to stiffer tests for safety and efficacy than DMSO, or which has passed with higher grades.

J. Harold Brown, M.D., of Seattle, has run several double-blind tests of DMSO in cases of acute musculoskeletal troubles—strains and sprains of the neck and upper and lower back, tendinitis and bursitis. Brown is a specialist in industrial (aerospace) medicine and, in this capacity, a consultant to the federal government.

Patients were given complete physicals, eye examinations, x-rays of the injured parts and several blood tests. Their histories were taken and their degrees of tenderness, pain and limitation of motion graded. The mathematical probability of error in results was defined by what are known as chi-square tests.

In a typical series, 13 or 15 strain and sprain patients on 80 per cent DMSO had excellent responses and the other two good, as compared with none on the placebo (10 per cent DMSO), and 9 of 15 showed a good or excellent response to standard treatment. The average number of days lost from

work during the first week after injury amounted to 1.2 for those on 80 per cent DMSO, 6.5 on placebo, and 4.4 on standard therapy.

In bursitis and tendinitis, 8 of 10 treated with 80 per cent DMSO had a good or excellent response, and so did all of the ten on standard therapy. None on the placebo reported benefit. The average number of days lost from work was 1.1 from the DMSO-treated, 3.1 of those on standard therapy and 6.2 on placebo.

No serious toxicity was seen.

That was one of scores of controlled studies ignored by DMSO's critics and the FDA.

I talked with Brown in his office in downtown Seattle on his "day off"—a Saturday in September 1970. Middle-aged, easygoing, he was interrupted constantly by patients who dropped in. He talked with them briefly, answered their questions, prescribed for a few, and sent each one away with a gentle pat on the back.

This is what he told me:

In 1965, a physician friend who had been using DMSO mentioned Dr. Jacob's article in *Northwest Medicine*. I had read the article, and I dismissed it as fantastic—a distortion of the truth.

Nevertheless, since my friend had success in using DMSO, I tried it.

The first patient seen had an ankle terribly swollen and so painful he couldn't bear weight on it. I swabbed DMSO on it. The swelling subsided while he was still in the office. He walked out. All this within one hour.

I decided to find out more about DMSO by becoming a clinical investigator for Merck.

I'm suspicious of all drugs. DMSO is no exception. But the longer I use it, the more enthusiastic I get. I think one

of DMSO's greatest values will be in rehabilitating the injured workman.

I don't share other investigator's great enthusiasm for DMSO in the treatment of arthritis. DMSO may work well on certain arthritic conditions; anything may, including prayer. We don't have a very good scientific basis for its effectiveness in arthritis.

I tried DMSO on probably a hundred cases of arthritis, and I obtained excellent results in many. They still say it was the only thing that gave them relief, but I'm still not convinced. There are psychosomatic factors affecting beneficially and adversely all chronic diseases, including arthritis.

In acute musculoskeletal conditions, it's different. DMSO gave relief within an hour or two; with the placebo, there was none. We tried to eliminate patients suceptible to psychosomatic influences.

DMSO was taken out of the hands of clinical investigators just before a good friend of mine, Dr. Jim Goddard, became the Administrator of the FDA. He inherited the DMSO problem. I knew him to be an extremely dedicated man, a very honest man, a sincere individual—one who would do his best to straighten out the bureaucratic tangle which the clinical investigators and people felt the FDA had not solved.

The severe adverse problems occurred in animals—and with tremendously high doses. The clinical investigations had been halted. Similar problems are found in almost every drug tested on animals for toxicity if extremely high doses are used.

The DMSO ban caused much anguish among my patients. For some I could not substitute comparable therapy. I provided DMSO as long as I had a supply. There was no humane alternative.

Sometimes the Oath of Hippocrates and our personal

professional ethics transcend other laws. We may be forced to decide which set of laws we must break. I would rather break the law of man than the law of God.

Following the discontinuance of treatment some patients reverted—perhaps not entirely—back to the physical situation before treatment. My phone was jammed with patients calling and asking, "When are we going to get more—when is it coming back for investigative or prescription use?"

Hardest hit were patients with chronic conditions such as the arthritics who had been benefited.

Dr. Jacobs is undoubtedly one of the most unselfish, unassuming, scientifically zealous individuals that I know. And it's my opinion that someday in the future this man's contributions may be recognized sufficiently to entitle him to be considered for a Nobel prize. I said this to Dr. Goddard.

Dr. Jacob has never asked for one thing for himself. He has never made one cent out of this discovery. It has cost him a young fortune out of what is by professional standards a meager income. He has suffered emotionally; he has been castigated. He has been almost Christ-like in his ability to withstand the sticks and stones of his enemies and critics, professional, political, and lay. He has survived only because he has the support of many colleagues and of his institution.

Dr. Goddard was extremely honest and dedicated. He had no thought of personal gain. He wanted to do a good job. But he had to talk out of two sides of his mouth; one as an administrator and a bureaucrat and one as a physician.

Many doctors doing investigative work didn't know all the law—that which pertains to the interstate shipment of drugs, for instance, or the requirement for voluminous clinical records. Many clinical investigators who deal with DMSO made similar mistakes. But they did not have the

name Jacob, the prime discoverer of its therapeutic benefits, the target for the FDA.

Dr. Goddard told me, the year before he left office, that he was amenable to submission of an IND from one of the pharmaceutical houses which had been doing a considerable amount of work with DMSO. He did believe that DMSO was worthwhile, especially in short term therapy in acute muscular and skeletal problems. He said, "Look, I'm ready for it. The pharmaceutical houses aren't sending applications to me. I can't go out and aks them to do it." When I proposed this to the pharmaceutical houses, they listened, but nothing was done. They said, "We are afraid. Our dealings have been with one of the other doctors in Dr. Goddard's office. If we go over his head and shoot the DMSO NDA directly to Dr. Goddard, we may lose out with the other drugs by embarrassing him. He could delay their acceptance for one reason or another."

I think the drug houses have learned to be patient with the NDA. Their very life, as a major industry in this country, depends upon their patience with bureaucracy.

Unless bureaucracy can recognize that DMSO has value, if only for the treatment of muscular or soft tissue problems, then all the scientific effort expended thus far will have been in vain.

Shortly before Christmas—on December 22, 1970—the United States Patent Office issued Patent Number 3,549,770 for "THERAPEUTIC ADMINISTRATION OF EFFECTIVE AMOUNTS OF DIMETHYL SULFOXIDE TO HUMAN AND ANIMAL SUBJECTS." The text, embracing thirty-seven claims, covered thirty-four columns of type. The attorneys involved said it represented the broadest approval ever given to a medical advance by the U.S. Patent Office.

The patent was issued to Robert J. Herschler of Camas, Washington, and Stanley W. Jacob of Oswego, Oregon, assignors, by mesne assignments, to Crown Zellerbach Corporation, San Francisco, California, a corporation of Nevada. Another patent, under the title "RETARDING THE GROWTH OF MICROORGANISMS WITH DIMETHYL SULFOXIDE," was issued simultaneously to Herschler, alone, as assignor to Crown Zellerbach; and in twenty claims it described DMSO's asserted ability as a single agent or in combination with antibiotics to control plant viruses and other industrial pests, particularly those resistant to other preparations.

Thus, with the Food and Drug Administration still banning DMSO, the Patent Office was honoring claims made for the drug by its investigators.

The patents were a long time in coming—more than seven

years—an extraordinary delay which some said was a measure of the pressure the FDA could exert on the Patent Office.

Patent No. 3,549,770 was one of ten applied for by Herschler and Jacob back in 1963. But, by virute of the vast sweep of pathology for which DMSO was cited, the detail of its administration, and the results achieved in numerous patients and animals set forth as examples, this was the most important of the patent applications. The other nine applications covered more specific and limited areas of use—in pain, inflammation, tissue damage, arthritis, respiratory distress, emotional troubles, infections, muscle strain and spasm, burns, skin grafts and vascular insufficiency.

The patent listed as DMSO drug forms lotions, sprays, ointments, paints, suppositories and injectable solutions. And it mentioned such methods of administration as topical, several injection routes, instillations and oral. (In the single therapy eventually permitted by the FDA, by contrast, DMSO could be used only topically, no more than 100 cc a day, for a maximum of thirty days—and only in horses, and, more precisely, non-breeding horses.)

In describing DMSO's wide spectrum as a drug, the patent preamble states that, "Unlike many other medicaments, it is useful in the treatment of apparently unrelated syndromes. The range of its activity and utility is such that it is not believed to be possible in the present state of medical knowledge in all instances to describe the activity utilizing classical medical definitions."

DMSO dosages mentioned in the patent range from 0.02 to 1.0 grams per kilogram of body weight in concentrations of from 1 per cent to 100 per cent; and the recommendations ranged from a single application to cure an occasional acute condition to virtually unlimited frequently over an indefinite period to control a chronic ailment.

The claims cited numerous clinical cases and, occasionally, animal experiments to illustrate DMSO's effects in scores of common serious clinical conditions.

The patent outlines in considerable detail the numerous forms of DMSO, and concentrations from 1 per cent to 100 per cent, diluted with water, ethanol, glycerine and other solvents, and in combination with other pharmaceuticals.

It mentions almost the entire gamut of routes of administration, and for those calling for special forms of DMSO, it tells how to compose DMSO "paints," nasal sprays, lotions, ointments (including creams and gels), suppositories and other forms. A great many salts and other chemicals are listed as ingredients which make the DMSO solutions more or less saline, or (as with glycerine) minimize skin irritation.

Part Four

"You know," Jacob said to me, "Commissioner Edwards is a very good man. We sat there in his office and talked until late. It must have been until six-thirty. He was in his shirt sleeves. He must be a hard worker."

Jacob, on questioning, said Edwards did not take back any of the things the FDA had been saying about DMSO, nor did he volunteer to undo the damage.

"He told me his hands were tied," Jacob explained.

It turned out that Jacob and Edwards didn't talk much about DMSO. Mostly, they discussed doctors and educators they knew. It was Jacob's first chat with an FDA commissioner who didn't threaten to scandalize, blacklist or imprison him. So, while he tended to like almost every human being, he was enthusiastic about Edwards.

Charles Cornell Edwards, M.D., successed Ley as FDA commissioner. With a broad midwest background, a flare for oratory, and long training and practice in the slickest, most up-to-date of business management methods, he brought to his office a new concept of administration and a platoon of professionals in modern management.

Edwards got his education in Colorado, topped off with a six-year surgical fellowship at the Mayo Foundation. He undertook a two-man practice in his wife's hometown, Des Moines, Iowa, whence he moved to a Washington, D.C.,

suburb. The AMA hired him as assistant director for medical education and hospitals; and from this job he moved over to the big management consultant firm of Booz, Allen and Hamilton of Chicago, where he became vice-president. He and his wife were regarded as well fixed financially; she was a Cowles—of the publishing family.

The commissioner was Jacob's age, dapper, smart, aggressive, and exuded the confidence of a man who had been around. He earned $36,000 a year in his government job.

Edwards could turn a neat phrase for every audience and on every occasion. As an expert in management, Edwards communicated a great deal—in speeches, in news releases and, occasionally, in interviews with co-operative newsmen.

Shortly after he came into office, I wrote Edwards—and called his office—to seek an interview on his attitudes toward DMSO and to ask, again, for any evidence of the drug's serious toxicity in humans. The Department of Health, Education and Welfare has a Public Information Regulation which defines the ground rules for satisfying the curiosity of the press and the public; and under this regulation, Goddard and Ley had consented to be interviewed. Edwards managed this matter neatly with a brief note: "I believe the Food and Drug Aministration has acted responsibly and in the public interest, according to the new drug requirements of the law. I will see that we continue to do so. At this time, I have nothing to add to our official statement, so an interview, as you have requested, would not be a wise investment of our time."

Early in 1972, an information officer of the deaprtment, HEW, intervened on my behalf. In response to this, an FDA press agent called me, and I told him I would like to interview Edwards either in New York or Washington but, if he happened to be coming to New York, as Washington officials often did, I'd prefer to tape the interview in New York. The HEW man called me. He said: "You know what FDA tells me? They say you are demanding that Edwards make a special trip to New York to see you."

That was ingenious management. I wrote that I would go to Washington any time that Edwards might designate. There was no answer. And that too was management.

Both Goddard and Ley had mentioned—after they left the government—that people tended to confound the job the FDA should do with the job it actually did. It seemed to be beyond the public's capability to distinguish purpose from performance. As a result, the agency gained unearned respect and escaped punishment.

The FDA deftly exploits this confusion with a steady stream of alarums, some of them "managed" by the large propaganda staff on and off the FDA premises. Some of the announcements are seasonal (banning electrically operated toys during the Yuletide) or oriented to a news event (proposed to lower the lead content of paints, following New York City's disclosure of many poisonings of children). Some of the events could be thought up by an imaginative management-minded man while dressing (poison in cosmetics, flammable wear), or in his kitchen (put iodide labels on salt and orange juice content on orange drinks, and how about the microwave or infrared oven?), or in the bathroom (label dangerous drugs, or, if that's been done too often, package them so children can't open them), or in the dentist's or doctor's office (raise hell—again—about unsafe x-rays).

The FDA has protected the public in recent years from literally endless perils; it had come out fearlessly (in newspapers and on radio and TV) against such products as clacker balls, abby walkers, pacifiers, rattles, dolls, darts, variegated foreign products, imitation milks, imitation creams, Mexican pottery containing leachable lead, mercury-carrying tuna, DDT-flavored farm products, fabricated meat, fabricated poultry, fabricated seafood, fabricated cheese. It recalled 8,800,000 sodium salt forms of vitamin C pills because the salt form was not specified on the labels. It proposed that human excreta and garbage not be dumped

from *new* railroad cars except at points designated by Edwards himself. (Dumping from *old* cars could be undertaken without instructions from Edwards.) Every now and then, the FDA made a list called GRAS, or foods "generally recognized as safe," although, according to the definition of GRAS, each item might be dangerous after all.

Because liquid drain cleaners containing more than 10 per cent sodium or potassium hydroxide are regarded as unsafe for children to consume, the FDA has required packaging that is hard to open. (Presumably drain cleaners of 9 per cent sodium or potassium hydroxide are GRAS.)

About thirty-eight cents of every dollar spent in retail stores goes for products regulated by the FDA—well over $240 billion a year, the FDA states. (Occasionally it gives conflicting figures.)

FDA condemnation of a product—whether capricious or warranted—can have severe economic consequences. The death from botulism of one man who ate contaminated vichyssoise bankrupted an old company called Bon Vivant; it turned out that no FDA inspector had looked in on their operation for four years preceding the tragedy.

A few cans of botulism-contaminated soup produced at the Paris, Texas, factory cost the Campbell Soup Company $10 million although no one was harmed. (The toxin produced by the bacterium Clostridium botulinum long has been an object of interest in chemical warfare; a teaspoonful or two, properly distributed, could kill everyone on earth).

The FDA gained page one publicity from the Campbell and Bon Vivant misfortunes. A couple of months later, just as the publicity had begun to wane, preliminary tests at the National Center for Disease Control in Atlanta indicated that some eight-ounce cans of Stokely-Van Camp green beans appeared positive for botulinum toxin. Again the FDA sounded the alarm, and again the agency landed on page one. This time, however, the food was okay. Edwards managed the faux pas in a speech before the National Academy of

Sciences' Institute of Medicine a few weeks later: "When a food or drug issue is raised to national attention, and very few of them are not, there are naturally instant pressures to act, regardless of whether science is ready and available. This was true some months ago in the case of the contaminated vichyssoise soup. It was equally true in a more recent false alarm over botulism in green beans."

There are numerous instances in which the FDA demonstrated monumental patience and resistance to pressure—often for years after science had adduced evidence of hazards in drugs and foods under the agency's regulations. There are such examples as:

1) Sodium cyclamate's causing cancer in mice:

2) The carcinogenic effect of saccharin;

3) Brain lesions in mice injected with monosodium glutamate; and

4) The relatively free and easy use of methotrexate, the anti-cancer drug, for conditions like psoriasis—although about twenty-five deaths have been attributed to its toxicity.

It took the FDA about eight months to act on a published report indicating that pregnant women treated with the synthetic estrogen, diethylstilbesterol (DES), sometimes bore girl babies who, when they grew up, developed a rare type of vaginal cancer. DES is used to fatten beef cattle and poultry, and human meat eaters are exposed to the residue. Despite the urging of the doctors who made the discovery, Edwards delayed publishing the facts until Rep. L. H. Fountain threatened to hold hearings on them. The commissioner said he had been closely studying the situation for eight months.

A couple of weeks later, Edwards moved vigorously against the many materials containing the anti-bacterial, hexachlorophene, which was widely used in vaginal deodorants, soaps, sprays and other cleaners and cometics. He explained that while there was no evidence of harm to humans from normal usage of the chemical, test animals and humans using it in "abnormal" ways (presumably in exces-

sive amounts) had shown elevated blood levels of hexachlorophene. Even medical men—or anyway some of them—thought that this time the FDA might be right, and they stopped using the antibacterial on babies. A week or two later, when twenty-two pediatric wards reported severe staphylococcus outbreaks, the FDA relented and then periodically changed the rules so that few, if anyone, could understand or obey them.

Under pressure of its numerous fiscal, political, publicity and other programs, the FDA had to ignore some troubles of individual citizens.

One such problem was the Ames case.

Jack Ames is the president and manager of the Home Federal Savings and Loan Association in Yakima, Washington. He spent a small fortune and dedicated a large part of his last twenty years keeping the breath of life in his daughter, Frances Lorraine Ames. Some of his letters had been dictated to his secretary; others had been typed by Ames himself late at night. Some of them covered six or seven pages with single-spaced type; and many of them were so graphic in describing the excruciating pain of the girl and the terrible anguish of the parents that they are now, years later, traumatic to read. A remarkable feature of all this correspondence is that each of the hundreds of communications was original; there were no slick photocopies or mimeographed enclosures to save Ames time and trouble. The only exceptions were "To-Whom-It-May-Concern" notes written by medical specialists certifying that regular DMSO treatments—before the drug was withdrawn—had not harmed Lorraine's eyes or shown any other signs of toxicity. These had been sent along to buttress the parents' piteous pleas for permission to apply DMSO to Lorraine's ailments.

When she was five years old, back in 1952, Lorraine had a series of illnesses, including measles, polio, post-polio encephalitis and mumps and then gradually a strange

neurologic disorder, which at various times had been given various diagnoses, perhaps most often multiple sclerosis. She suffered recurrent high temperatures, loss of balance, impaired eyesight, loss of bladder control. She was immobilized periodically. And always there were the recurrent overwhelming pains of contractures and from other sources.

Lorraine responded fairly well but briefly to cortisone. She was given other drugs that might conceivably help her; but they were of little use. Then, in July 1964, Ames read a story about DMSO in *Life;* and, through Jacob's good offices, Lorraine's doctors got some and applied it. "DMSO was very beneficial when no other medications would help," Jack Ames later said. "It was not a cure. But it was extremely valuable in alleviating the inflammantory part of her illness and in reducing the extent of her contractures and the pain associated with them."

When the FDA in November of 1965 forbade further use of DMSO, Ames entered upon his tireless campaign to persuade the FDA to let Lorraine's physicians treat her, preferably by intramuscular injection. He bombarded with heart-rending appeals such FDA dignitaries as Drs. Goddard, Hodges, Sadusk and Kelsey and Mr. Kirk. He pleaded with congressmen to use their influence on his behalf—including Senators Magnuson, Jackson, Hatfield, both Longs, and a long list of Representatives, including Wyatt, Morris, Catherine May, Fountain, John Jarman and Edith Green.

Most of the congressmen took time off to inquire into the DMSO situation and to write a, usually not very encouraging, note to Ames. The FDA people also answered the letters and telegrams that Ames directed at them; but most of their responses were businesslike, impersonal, vacuous, completely negative and they ended with what seemed a mocking line: "If we can be of further assistance, please advise."

Through intervention by Catherine May, who was Ames's congresswoman and an old family friend, Ames finally was granted an inteview with Goddard; and at long last his physi-

cians were given permission to use DMSO by skin administration on Lorraine, but on condition that regular highly complicated physical and chemical tests be run. The tests proved impossible and unacceptable to physicians and drug houses after six weeks.

Ames described his experiences and his feelings in a letter to Congressman John Jarman on May 6, 1968:

"The enclosed correspondence I am submitting is a sample of the frustrating experiences I have had with the FDA. It is one thing to administer a law and another to completely, for all practical purposes through evasive replies, ignore an individual with an obvious critical problem."

He charged that FDA officials had dodged his telephone calls. He said that DMSO had proved safe and helpful in his daughter's case, and he blamed the FDA's feeling of "vengeance" toward Jacob for its unavailability for seventeen months.

"I am certain," Ames told Jarman, "that you or any member of your committee would hate to watch, as my wife does, day in and day out our young child's (now young adult's) legs jerk with spasms, the knees cross over and pull up, the lower leg contract until it is against the back of the upper leg, the femur pull out of its hip socket, the voice diminish to a whisper and swallowing become difficult with choking on the first bite, a fairly often occurrence. The muscular control of our daughter's bodily functions, her ability to think and express herself is being encroached upon ever so relentlessly by her neurological illness."

Ames said one of Lorraine's neurologists had told him that a foreign drug capable of releasing some contractures was being evaluated by the FDA.

"My feelings would be indescribable," he said, "if such a drug had been held back in a 'bureau drawer,' so to speak, until our daughter passed on."

When I heard from Ames in September 1971, Lorraine was still clinging to life but had been in the hospital re-

peatedly with a high temperature and possibly either kidney trouble or septicemia.

The FDA was not accepting the blame for Lorraine Ames's difficulties or the miseries of the multitudes of others who stood to benefit from DMSO. Paul A. Pumpian, Director of the FDA's Office of Legislative and Governmental Services, put it this way (in this case, in a note to Senator Jackson on May 19, 1967):

"While the Food and Drug Administration may permit a sponsoring pharmaceutical firm to make DMSO available for clinical testing, we can do so only after receiving a proposal for such use from a drug firm willing to accept the responsibilities described in the Investigational Drug Regulations. Of course we cannot require any pharmaceutical firm to sponsor a clinical investigation, nor can we require them to make the drug available for such use." He enclosed a copy of the regulation. "The monitoring guidelines were established for patients' protection," he said.

A year earlier, M. D. Kinslow, then Director of Legislative Services, used pretty much the same statement in a note to Jackson and added this thought: "We can certainly understand Mr. Ames's deep concern about obtaining aid for his daughter; however, to lend any encouragement to the use of DMSO in this manner and for this condition would be premature as well as an interference with the doctor-patient relationship." Kinslow overlooked the fact that Lorraine had been on DMSO with good therapeutic results and no serious side effects for eighteen months.

I can't believe that there was a note of sly humor in some FDA communications. There was the line, for instance, in a note written by Dr. William J. Gyarfas of the FDA to Jack Ames, after Ames had been bombarding the FDA for years on behalf of his desperately ill daughter: "We appreciate your continued interest in the investigational new drug DMSO."

Pumpian said in a letter of Senator Jackson: "We appreciate Mr. Ames's continued interest in the investigational new drug DMSO, as well as his concern for the general area of drug testing. If we can be of further assistance, please let us know." Pumpian also pointed out in this letter that he had let Ames know that "we are still, as in the past, most willing to authorize use of DMSO for his daughter under an appropriate investigational protocol."

Congressman Wyatt, who had championed DMSO, reported that the FDA had relaxed its rules, and "it appears that the persecution of DMSO has ended."

At this time scientist-friends of mine were experimenting with blood fractions which made spontaneous cancers in mice disappear overnight. They had one major problem: the mice weren't standing up well under the trauma of injections.

I got on the telephone to see if I could get a little DMSO for my friends. DMSO might dissolve and transport the anti-cancer preparation through the mouse skin and eliminate the trauma.

A supplier, called K and K, told me to try B and B, who told me I'd have to get a release from the Federal Bureau of Narcotics and Dangerous Drugs, who told me the bureau recently had been shifted from the FDA to the Department of Justice, who referred me to JO 8-5000, the telephone number of the FDA in Brooklyn. I explained my mission:

FDA This DMSO is strictly for laboratory research animals?

I This is for mice.

FDA Yeah. Laboratory research animals. Right?

I That's right.

FDA There is no impediment to the use of the material for use in laboratory research animals. Of course, if it's to be used, uh, clinically, on animals, that's a different story. See? But from what you've described, this is simply usage in laboratory research animals. Right?

I Yes. It's clinical to this extent: These are spontaneous cancers in the mice.

FDA Spontaneous cancers, huh?

I They're not induced.

FDA I see. It might be clinical then, huh?

I Well, what do you think?

FDA But it's strictly laboratory research there. I mean, you're not treating the mouse; you're determining what it'll do in the mouse if it's used in the human. Isn't that correct?

I They seem to be clearing up these mouse cancers by injecting the stuff.

FDA Yeah.

I So it could be that they're using the DMSO to cure cancer. Would that be permissible?

FDA Then you go into another area, in which case, investigative statements would have to be obtained, you know, there would have to be a sponsor, whoever's sponsoring this; and of course the sponsor can be his own investigator, and then he would have to notify the Food and Drug Administration of his intended work.

See? I mean, you know, this is another area. In other words, this would be in the area of *clinical* investigation in animals.

I If you cure the cancers, it's clinical?

FDA Well—it could be construed that way, you know.

I You can use DMSO to cause cancer, but you can't use it to cure cancer. Is that it?

FDA Well, there is no such thing as you can't use it. You can use it. The government—the regulations aren't stopping research, you know. It's just a matter of approach here. If it fits the bill in, ah, you know, the usage in—well, I'm repeating again—in laboratory research as opposed to clinical investigation in animals. And it seems to me like we have here a sort of borderline case, because here you are causing cancer and also trying to eliminate it.

I We're not causing it.

FDA As we talk here, you see, you are curing something in an animal, but the context in which the regulation is written here is that then you would be using this in the animal all the time. But you're not going to be using it. You're just using it for testing in that animal. You're not going to, in other words, if it succeeds, you're not going to, let's say, take DMSO or recommend it for treatment on tumors in this particular species of mice on a commercial scale. Now, that's not your intent, is it?

There was more—much, much more. Finally, I asked where I could get DMSO if I met all the FDA's conditions. He told me to look in the yellow pages. I was back where I started—with K & K, and B & B. And I gave up.

Congressman Wyatt's optimism didn't seem justified.

While the FDA had succeeded in discouraging almost all respectable and responsible research with DMSO, it was as effective in snuffing out experiments by non-professional people as the Volstead Act was in discouraging drinking.

I once talked with a woman—let's call her Minnesota Mamie—who was a non-professional practitioner of the healing arts.

This is the way her story came out on tape:

I've used DMSO for almost everything under the sun. We cured a man who hadn't been able to have his shoes on for three years. I got him with his shoes on by using DMSO. He had gout. He also had emphysema, and the DMSO helped that greatly. We used it by mouth and by sort of a spray. But I used it all over his chest and his back and his forehead. And at nighttime just a little bit around his nose. I treated him for nine months.

I gave him about three drops to a teaspoon of water. Three times a day. Dr. Jones nearly died when I told what I did. He had some cattle, and he had to breed a cow very quickly. The animal that he was using and the cow weren't uh—uh—compatible. So I said, "Oh, for heaven's sakes, here's the balance of the DMSO. Use it." Just kidding, more or less. But it worked fine.

A friend of mine who's a little old lady, she's got money that rolls out of her ears, but she has this sore on her leg that she couldn't get rid of. And the doctor couldn't do anything about it. And I kept yelling at her, "DMSO, DMSO, DMSO." She thought I had holes in my head, and so did the doctor. I had at this time about a quarter of a cup left, and I applied it, but I used castor oil with it. I made a mixture of castor oil and DMSO and put it on. And the sore went away.

Stanley Jacob had been told by several sources that DMSO was being widely bootlegged.

"A lot of people receiving DMSO from other than FDA-approved sources are getting a low-grade material," he said. "It scares me.

"Some veterinarians are using crude material. The FDA, however, has permitted use of high-grade DMSO, with restrictions, in horses. Veterinarians are using it in other species, as well, and this is understandable. But they're also using low-grade DMSO. A distributor told me that Syntex is supplying no more than ten per cent of what is being used by veterinarians. The other ninety per cent is bootleg."

Jacob, following a talk before the Portland Commerical Club, was told by a port authority officer the biggest product smuggled into Portland was DMSO. Most of it came from Japan.

A pint of DMSO, even contaminated industrial grade, brought twenty dollars and up, although the legitimate price was still as little as thirty-five cents a pint, in thirty-five-gallon-drum lots. With purifications to reagent grade—that is, about 99.5 per cent pure, or good enough to be used in a chemical lab—DMSO sold to industry for anywhere from fifteen to thirty-five dollars a gallon, depending on the avarice of the seller and gullibility of the buyer. Crown sold spectral, or medical, grade DMSO, the purest of all, for $1.25 a pint to Syntex, which then diluted it with 10 per cent water and sold it to vererinarians for $10.85 a pint.

Who—or what—was the FDA, the *bête noire* of Stanley Jacob and DMSO? It was an agency possibly unique in the history of government—any and all government. It was as incredible in its way as Stanley Jacob was in his—or DMSO in its.

It has been criticized bitterly by many familiar with its operations—aggrieved individuals, a large part of the scientific, medical and popular press, Congressmen, commissions and committees appointed to investigate the agency, and the highest officers of the bureau itself.

Ley told the *New York Times* after he left the FDA:

"The thing that bugs me is that people think the FDA is protecting them—it isn't. What the FDA is doing and what people think it's doing are as different as night and day."

In May 1969, Ley had appointed a "Study Group on FDA Consumer Protection Objectives and Program" which later became known as the Kinslow Committee because the chairman was Maurice D. Kinslow, who headed up the FDA's Baltimore office. The members numbered seven, with three being doctors and Kinslow and three others being "lay." All were officials of the FDA.

The Kinslow Committee in eleven weeks put together a forty-six-page report which recommended drastic changes in the FDA organization and services. While the report was regarded as a ploy to induce Congress and the Administration

to pour more money into the FDA, it made it clear that the FDA was not doing the job that should be done to regulate the more than 60,000 food, drug and cosmetic firms with annual sales of more than $130 billion.

The report indicated that FDA was neither informing consumers nor enlisting their help as it should. It said the FDA was failing to curb lies in advertising, limit filth and other contaminants in food, work with allied agencies, check on the safety and efficacy of drugs, work closely with scientists, doctors and industries, and investigate hazardous products. The agency lacked adequately trained scientists, it said.

The Kinslow report was one of about a dozen critiques of the FDA produced at about this time. And it was one of the very few which showed some sympathy for the FDA. Nevertheless, the careful reader had no difficulty detecting that all was not well with the FDA. The FDA itself was saying so.

The FDA and some of its officers have been accused of lying, cheating, police state tactics, bribe taking, medical quackery, atrocious scientific judgment, being soft on narcotics, censorship, blacklisting, blackmailing, conspiring with Internal Revenue Service and other federal agencies to "get" the critics, driving small drug houses into bankruptcy, pandering to major drug houses, boondoggling, inflicting needless discomfort and death on sick people, harassment, intimidation and numerous other sins.

The recent history of the FDA has been reviewed critically in *The Dictocrats, Our Unelected Rulers,* a free-swinging exposé by Omar V. Garrison, and *The Chemical Feast,* by James S. Turner, a detailed, documented report assembled by Ralph Nader's Study Group.

One other official report gave a rather clear picture of the agency. Six prominent men in the fields of science, medicine and education, comprised the FDA Ad Hoc Science Advisory Committee, which was to "review and evaluate the total scientific effort of the FDA and to advise the Commissioner

on aspects of FDA's science activities that, in its judgment, warrant improvement."

That committee was set up by the commissioner, who was not known to flagellate himself and his associates. The committeemen were not trained and tough investigators but men of culture and professional standing—the report was remarkably candid. The members were Marion W. Anders, D.V.M., Ph.D., Associate Professor of Pharmacology, University of Minnesota; Berwin A. Cole, Ph.D., Deputy Associate Commissioner for Science, FDA (Staff Director); J. Richard Crout, M.D., Professor of Pharmacology and Medicine, Michigan State University College of Human Medicine; Willard A. Krehl, Ph.D., M.D., Professor of Preventive Medicine, Jefferson Medical College; Roy E. Ritts, Jr., M.D., Professor of Microbiology and Immunology, Mayo Graduate School of Medicine, University of Minnesota (Chairman); and Lauren A. Woods, Ph.D., M.D., Vice-president for Health Services, Virginia Commonwealth University.

The Ritts Committee, as it was called, made it clear that the FDA was not all bad—nor all good. "Thus one can find in the FDA certain laboratories with advanced technology, good morale, and high productivity which give every impression of being first-rate by the most rigorous standards," the report began. Having demonstrated fairness, the report continued: "On the other hand, one can also find laboratories so poorly managed that scientists seem unable to describe their work coherently or produce interpretable data books containing their findings."

The report, in fifty-six pages, single-spaced, listed as among the impressions recorded during one year of study:

> In many FDA laboratories, the general scene is not charged with any sense of excitement or even great industry . . . the FDA has long favored the compliance branches over the scientific branches . . . the FDA has

not engaged in adequate central planning; planning often failed to include opinions of scientists . . . some regulatory decisions are as defined by law, even though they may not be consonant with scientific data or opinion . . . because of erratic shifts in planning, administrative reorganizations, and new crises, scientists often must suspend or abandon ongoing work in favor of new projects . . . arbitrary administrative rulings on scientific activities are frequently made by non-scientists . . . certain scientists, instead of carrying out assignments, pursue research in line with their own interests or what they think is best for the agency, and management and central planning are so bad that self-assignments are hard to detect or correct . . . frustrated scientists take their incomplete or preliminary findings directly to the public . . . the scientific environment is encumbered with a curious aura of secrecy, an atmosphere of non-communicativeness between scientists within the agency and in universities and industry, commonly explained away as protecting trade secrets or lack of understanding of FDA problems by outside scientists.

The committee even hinted broadly at perilous hanky-panky jeopardizing the nation's drug and food supplies, when it said, "The Committee is in no way persuaded that the scientific basis for regulatory decision-making should be modified by consideration of economic or political factors."

Almost every scientist interviewed by the committee acknowledged that managerial and communications problems were "long-standing and widespread," according to the report.

Considering the punishments meted out by the FDA, one comment carries a particular poignancy: "The Committee was disturbed to discover that the FDA did not have a systematized record keeping system for laboratory work. There was no evidence that laboratory data were being recorded in such a way as to be secure from misplacement or

alteration, or to permit ready retrieval . . . The Committee strongly recommends that the Commissioner remedy this situation immediately."

The committee found that some of the FDA councils of outside scientists had not been used at all, that others were never told what to do.

The committee found that "serious deficiencies exist at all levels" of the contracts for research (amounting to more than $6,000,000 a year) which the FDA farmed out to scientific organizations. It found the FDA guilty of bad or negligible performance in contract planning, setting priorities, soliciting bids, reviewing contract proposals, supervising research activities, maintaining a budget, appointing project managers, and in not permitting the scientists to report research.

The committee concluded that FDA District Offices are operated as "the compliance arm of the FDA" and that the scientists and their laboratories are oriented toward police work—surveillance and analytical procedures. As a result, the selection of food and drug samples for testing is sketchy and the procedures antiquated and cumbersome, the productivity per scientist low, with a preponderance of senior scientists (and dearth of technicians) who do menial work and inferior scientists who work for the relatively low pay of the FDA and tolerate restrictions against publishing research results.

One of the dangers of the FDA field setup is posed by the drugs added to animal feeds which humans ingest in meat and poultry. The widely differing estimates of drug residues in meat and poultry, the committee stated, indicate that "there may exist a situation of possible danger to the public and potential embarassment to the government."

The committee expressed trepidation at the prospect of the FDA's announced intention of expanding its jurisdiction over foods—adding to its present badly done job of monitoring them for contaminants the additional task of passing on their nutritional qualities.

The report said, "The Committee was dismayed to learn

that the FDA does not have accurate information at any point in time on the identity and amount manufactured of all drug preparations, both ethical and proprietary, currently on the market in this country." It found fault with the FDA's inadequacies in statistics and in epidemiology.

The report said the processing of applications for the testing and introduction of new drugs "is slow and erratic, demands for data may be scientifically unjustified, some reviewing officers make rather rigid and arbitrary decisions while others have trouble making decisions at all, and interpretations of policy vary from reviewing officer to officer."

The report noted charges that university investigators faced unreasonably requests which hamper research, that applications were often poorly documented, that obfuscation was frequent, and that many studies were scientifically poor. "These complaints seem to go beyond the expected grumblings of the regulated, and their persistence through the years implies the presence of chronic unsolved problems," the report stated.

The committee, commenting on the unfavorable reputation of the FDA scientists, attributed it to the belief that the safest course for the medical officer to follow is to be negative, since he will then stay out of trouble. It added, "The toll is indirect but real: difficulties in recruiting top-flight scientists into the Bureau of Drugs, diminished credibility with physicians in practice, and a low level of respect among university and industry scientists." It said the FDA medical officer all too often had "neither research experience nor prestige among his scientific peers; nor are his judgments viewed by his fellow scientists as scientifically sound."

The report described handwritten documents, typewritten communication days and weeks behind schedule, crowded offices, desks in waiting rooms, the lack of training programs. It pointed out that some studies showed 25 percent of drugs then marketed were substandard.

The committee said, in an embarrassed sort of way, that

the AOAC (the Association of Official Analytical Chemists) was the beneficiary of an affectionate financial and footsie-type relationship with the FDA. The AOAC is an independent scientific society of the United States and Canada whose principle role is sponsoring the development and testing of methods of analyzing pesticides, food additives, drugs, animal feeds, cosmetics, liquors, beverages, fertilizers, hazardous household products, air and water pollutants, and the like. The facts that the FDA puts a lot of money into the AOAC, that most of the AOAC's associate referees (298 of the 585) were FDA employees, and that the relationship could suggest financial advantages to both the FDA and the AOAC people occurred to the committee. With restraint, the report did not carry the ugly words graft or bribe or even moonlighting. The report did say, however, that:

> As in issues of conflict of interest, where the appearance can be as damaging as the actual guilt, there are facets of the AOAC-FDA relationship which in the hands of the poorly motivated could embarrass FDA. As examples, certain FDA employes whose titles, grades and job descriptions indicate otherwise actually spent significant portions of their official working time on AOAC business, in the capacity of AOAC officials; at times one can be easily confused as to when they operate as AOAC officials and when as FDA employes.

It mentioned that the FDA gave the AOAS space, supplies and facilities; but the AOAC did use a non-FDA address, "even though the residence of the AOAC in FDA is common knowledge," as the committee puts it. The committee added that "these facts give the *appearance* of subterfuge and an interlocking directorate."

The Ritts Committee report may have clarified one phenomenon: Despite the FDA's numerous nominal house cleanings, nothing really changed. The Ritts Committee said:

The recent reorganization was but the latest in a series of such activities in recent years, each usually accompanied by an infusion of new management at the highest levels. The Committee detects that this has sometimes in the past contributed to poor morale. Furthermore, there appears to have engendered an attitude on the part of some that nothing changes very much at mid- and lower levels in spite of such management changes at the top. This view is supported by the observations that the middle management of science of the FDA has been very stable over the years. After a reorganization, the same names are seen, but in different capacities.

With increasing vehemence over the years, Jacob's friends advised him to stop the nonsense and claim a share of the royalties from his patent rights. He had remained adamant in his refusal on the grounds that the commercial aspect might impair DMSO's chance to win the FDA's acceptance.

Jacob's friends advanced these arguments:

1) He was broke and deeply in debt.

2) He needed funds to fight for DMSO.

3) What would happen to his employees and his able associates, if the economy wave sweeping over research institutions would strike his own projects?

4) What would happen to DMSO, to his patients, to his career in research if he lost control of the fruits of his labor?

The arguments were telling; the last seemed to stagger him. The omission of his name from bibliographies in papers on DMSO and even from the forty references cited by Syntex in announcing the advent of Domoso, its veterinary DMSO, reminded him that scientific credit can be short-lived.

A series of events brought the patent royalties matter to a head late in 1970. The medical school faced a financial crisis; the state Board of Education was reported ready to distribute medicare and other funds, not only to the medical school, but more generally. It was becoming clear that the royalties from DMSO might be handled in a similar manner—despite Jacob's desire to see them used by the medical school and, especially, by the Department of Surgery.

The first royalties from Syntex's veterinary Domoso soon would be due. Friends warned Jacob that while the state would look with favor now on the idea of splitting royalties with Jacob, this generosity well might subside when real money was at hand. As his chief, Dr. William Krippaehen, put it: one third of nothing is nothing and easily given away; one third of something is different.

Herschler, too, faced a crisis. Crown had given him a check for $500, presumably "fair compensation" for one of his patents—one for DMSO anti-perspirant preparation. (Jacob said this patent had no utility—"it substituted one odor [DMSO] for another [body, underarm, etc.]"—and would have none until DMSO was rendered less smelly.) Herschler was not cashing the check, lest his acceptance of it be considered as approval of the arrangement. Meanwhile, without a laboratory, or a secretary, or duties, he was passing time in the Crown library. He was given more $500 checks for more patents; and these too remained uncashed.

Herschler saw Jacob's lawyer, Norm Kobin, and inquired about the possibility of diverting some of the royalties into a non-profit organization to be called Search, Incorporated. Under such a setup, Herschler would like to explore other plant chemicals, and Jacob would test DMSO on human diseases which were incurable, rare and so medically unprofitable that drug houses would not invest in their research.

At the urging of his associates in surgery and others at the medical school and at the invitations of Freeman Holmer, Vice-Chancellor of the Oregon State System of Higher Education, Jacob on June 17, 1971, finally asked for 30 per cent of the Board's royalties for himself and 70 per cent for the medical school.

The state, acting through its Board of Higher Education on behalf of the University of Oregon Medical School, readily conceded in a flurry of "hereinafter's" and "whereases" and "now, therefore," that Jacob, as co-inventor (the other

co-inventor was Herschler), would receive 30 per cent of the state's net patent income.

The patent rights estimates were running as high as nine and ten figures. With about 100 different patents applied for or granted in various countries, Jacob said that Hershcler and he would share, as partners, all money either man derived from DMSO, and if it were enough, both would spend the rest of their lives in research of potential benefit to mankind.

I asked Jacob if he had applied for a patent on DMSO's ability to restore hair. He said he had not. This could be one of the most lucrative of the DMSO patents.

"There is no doubt now that DMSO stimulates hair growth," he said. "It has done so—very slowly to be sure—in almost every person we've tried it on.

"We've been applying DMSO for the last eight months to save a gangrenous hand," he said. "The patient still has dry gangrene, but pictures of the two hands show that the one receiving the DMSO has significantly more and longer hair growth than the other hand.

"At meetings, the veterinarians report the hair grows on animal limbs treated with DMSO better than on the untreated limbs."

While much of the population was sleeping off Saturday night celebrations, Dale Moon and Dr. Latham Flanagan, Jr., rose from their beds at Timberline Lodge, dressed, ate hastily, packed and at a quarter past three on the morning of Sunday, December 27, 1971, set off in a light but steady drizzle that soon turned to sleet and snow. God willing and the weather permitting, they would struggle to the 12,245-foot top of Mount Hood, see what was to be seen, descend and be back at the Lodge before 4:30 P.M., when the sun was to set.

The weather was a party to no such program. Stinging snow was blown by eighty-mile-an-hour winds when the men reached the summit ten hours after they had set out. From their panoramic perch atop the world, they could see a distance of about fifteen feet. It took five days to fight their way back to the lodge. They were frostbitten, dreadfully hungry and too weak even to shiver. They were taken at once to the medical school.

Krippaehne, Chief of Surgery, thawed Flanagan and Moon out. Jacob called the FDA in Washington and talked to an FDA physician.

"Of course you may apply the DMSO, if in your clinical judgment it is indicated in this emergency," said the official.

"How about the IND applications?" Jacob asked.

"Make it out at your convenience, and send it in."

Jacob was overjoyed by the ease with which the matter was resolved.

Flanagan and Mr. Moon did beautifully. Their frostbite, moderately severe, cleared up in a spectacular way.

"The most memorable part of all was discovering a real physician in the FDA," Jacob said. He declined to identify the doctor for fear of getting him into trouble with his superiors.

If the FDA relaxed its rigid rules on any other occasion to provide for DMSO treatment, the evidence is hard to find. Nevertheless, piteous appeals were directed by a multitude of patients to the FDA, directly or through congressmen from all parts of the United States. A small sampling included:

I'm quite sure my husband is alive today because of this drug. In March of 1963 he became so bad with gout, he could not raise a hand. He was flat on the hospital bed for 5 months. Every joint in his body was twice its size. He was on strong morphine which could not keep the pain down. Our doctor held little hope for his life. We heard of DMSO and got him to Portland. On DMSO he started improving and at the time the FDA cut off all activity with the drug he was on his feet again and completely without pain. Oh, please God, if Dr. Goddard could only suffer for just one month as my husband suffered for years.

My brother has arthritis of the spine. He is in pain and bedridden more than half the time. When he is treated with DMSO, he is able to lead a normal, active life. If you could live with us for even a few hours, you would understand. The mental anguish of my mother, my brother's wife, and other family members is not a subject I can describe on paper. Just ONE application of this cheap, *safe* DMSO changed my brother from a grimacing patient into an active pain-free man in exactly *30 MINUTES!* This could

come under the heading of "too bad—sad case" *IF* my brother were an isolated case. Multiply him and my family thousands of time, *THEN* think what the FDA's Divine Right of Kings law is doing to thousands and thousands of helpless patients and their families.

My son-in-law suffers from scleroderma. His children weep; my daughter weeps and prays; I weep, and pray, and write letters. Someting *must* be done for him and thousands of agonizing citizens. Think how much of our strained budget could be saved by healing these good people and returning them to the land of the living—earning money, paying taxes, being useful citizens once more.

I had arthritis for four years gradually getting worse until I got to the place where I was in such agony day and night I was almost at my wit's end. I had shots in my shoulder joints, x-ray treatments, physical therapy, even a shoulder irrigation, all to no avail. Two doctors—an orthopedic surgeon and an internist—finally said there was nothing more they could do for me except prescribe pills—Empirin codeine which in my case gave only short relief. I heard of Dr. Jacob and went to visit him. I knew DMSO was a brand new drug on an experimental basis, but I would have been willing to try it if it killed me. Almost from the first I began to get relief. Now I am on my feet well and active. I do all my own work and gardening. I have never in my life wished ill of anyone, but experiencing the caliber of this agency (the FDA), I wish every last one of them would suddenly have an attack of acute arthritis so painful you could hear them yell from there to here and have to beg for the only drug ever discovered that could give them real help.

Both as a scientific worker and as a patient with a disease for which no effective recognized therapy exists, I

have become increasingly concerned about the manner in which new drug applications are being handled. DMSO has been virtually regulated out of use by the most stringent restrictions on the sale, shipment and use, and utterly prohibitive paper work requirements for investigative use by clinicians. This is in spite of the fact that no authenticated cases of injury to humans have been documented. It would appear that FDA's cavalier treatment of DMSO (and the patients who desperately need it) stems from (a) the publicity it received as a wonder drug in the public press during 1964–65 and (b) the utter impossibility of writing a use authorization at once sufficiently broad to cover the demonstrated indications and dosages and sufficiently narrow to satisfy FDA's concept of its role as the sole arbiter of drug usage in the United States.

In obtaining DMSO for me, you have handed my life back to me, and I am, together with my entire family, grateful. I'm still running a fever, but it's coming under control. My living would not have been possible without your help.

(Pumpian of the FDA, when asked about DMSO, wrote to one senator: "No drug in recent times moved more rapidly from novelty to nostrum than DMSO." When another senator requested amplification, Pumpian assured him, "By our reference to DMSO as a 'nostrum' we were not referring . . . to a 'quack remedy,' which is one of the definitions of the word 'nostrum,' but rather we used the word in the sense of one of its other definitions—that of a 'questionable remedy.' "

Hope did not die easily or soon with some patients. One woman wrote Jacob in 1971:

My husband has been an experimental user of DMSO

for four or five years, having been introduced to it by a Los Angeles doctor. When we went to him about six years ago, we were at the depths of despair. My husband already had had disc surgery ten years earlier—which was completely un-successful—and has been suffering from severe back pain ever since. He shuttled back and forth from doctor to doctor—from physical therapist to psychiatrist, from hypnotherapy to self-hypnosis, constantly existing on drugs, with nothing giving him permanent freedom from pain.

At the doctor's suggestion, he became an experimental patient for DMSO, and it became his staff of life. He used it for four or five years with complete success, his pain mysteriously or miraculously gone within 15 to 20 minutes from the time of application. (He had many times been so crippled and bent and in pain that he lay on the floor, unable to get up until I applied the miracle liquid to his body. He incidentally never had any side effects.)

And then one day we were told that DMSO was taken off of research and would be available no more.

Dr. Jacob, we are again at the depths of despair. My husband is again crippled and in constant pain. He is about to quit his job.

He would like to become one of your experimental subjects for DMSO. Desperately—

Part Five

Richard D. Lyons reported, in a series of three articles beginning in the *New York Times* of March 14, 1977, that the FDA within the last ten years "evolved from amorphous obscurity deep within the capital bureaucracy into both the world's paramount regulator of consumer goods and the Federal Government's most criticized, demoralized and fractionalized agency."

Among the points made by Lyons were these:

*Top FDA positions remain unfilled for long periods and the leaderless departments "drift and founder";

*within the last three years the FDA was subject to more than 100 Congressional investigations, 50 highly critical reports by the General Accounting Office, a series of internal investigations by FDA staff committees;

*employees complained before Congressional committees about their superiors, thus inviting more harassment, intimidation and reversals of their official findings on specific foods and drugs;

*special interest lobbies went to Congress and contacts in the White House to have FDA decisions overturned, while

*new drugs piled up, new foods with new additives went on the market, and new devices stagnated in an enormous backlog.

Under these conditions, what could the frustrated employees do?

Dr. J. Richard Crout, Director of the Bureau of Drugs, once told a Congressional committee that in the FDA there was drunkenness, absenteeism, fights in the enormous documents room and spitball throwing. Members of the professional staff were called "retreads" and "has-beens," he said.

Division directors and their staffs engaged in "a kind of behavior that invited subordination," Crout said. He added, "People littering in corners, throwing spitballs—I'm describing physicians. People who would, let me say, slouch down in a chair, not responding to questions, moan and groan with sweeping gestures, a kind of behavior I have not seen in any other institution as a grown man."

It is not as though nice things are never said about the FDA. For the life of me, however, I cannot recall hearing anyone with a good word who was not in the employ of the FDA. Sherwin Gardner, the outgoing Acting Commissioner of Food and Drugs, was one of these. In a letter to the *Times*, he took issue with Lyons's articles and an editorial. "Nobody Loves the FDA."

Gardner pointed out that the "relatively small" FDA, with a staff of 7,000 (triple what it had been 15 years ago) and a budget of $253 million (a tenfold increase in 15 years) is expected to regulate a $200 billion product manufactured and distributed by 100,000 firms. He contended that the FDA is not demoralized. "There are some dissatisfied employees," he said; "that condition is bound to exist in such a complex organization. The conclusion that nobody loves the FDA is a bit disconcerting, but is probably on occasion true."

The FDA has absorbed unremitting abuse for many years and from many quarters. And it has thrived on it. Its powers—for good or evil—have increased year after year, and so has its budget. In situations where a maximum of only two decisions seemed possible, the FDA has stretched that maximum; it did so by repeatedly reversing itself as it was buffeted one way and another by its numerous critics or wooed by industry. Sometimes it found a compromise solution to problems.

For years after Dr. George T. Bryan, a University of Wisconsin biochemist, reported that both cyclamate and saccharin caused bladder cancer in laboratory animals, the FDA remained unmoved. Eventually, however, public pressure and confirmation of his findings became greater than industry pressure. First, cyclamates became the subject of debate, and this may have proved to be the beginning of the end for unrestricted use of artificial sweeteners. Saccharin was next; and for several years a sometimes bitter battle ensued with the diet food and drink and pharmaceutical manufacturing industries and diabetologists on one side (favoring sugar substitutes) and the FDA and some consumer groups on the other. Assorted politicians, environmentalists, physicians and members of the public were in the middle. A poll by a consumer marketing group resulted in a two-to-two vote by the public against banning saccharin.

The situation was complicated by two legal points governing FDA actions: 1) a 1958 Delaney Clause in Food and Drug Law amendments banning any substance in food that causes cancer in humans or animals, and 2) the 1962 Harris-Kefauver amendments requiring proof of safety and effectiveness of drugs before they are allowed on the market. With Solomonlike judgment, the FDA called saccharin a drug, permitting its over-the-counter sale, like aspirin or mouthwash, with a label warning that it might cause cancer. This decision called for barring commercial producers from incorporating saccharin, as they were doing, in many categories of groceries; consumers thus were forced to buy the additive in bulk and put it into their own foods.

Although the saccharin problem was not settled, the FDA reached what some felt was a fair and reasonable conclusion: Diabetics and fat people could have their sugar substitute and take their risk with cancer—evidently a mild one, because it took a lot of saccharin to produce a relatively few rat tumors—and the general public was relieved of the almost compulsory eating of the saccharin put into their food by the industry.

But the decision changed few attitudes and left a lot of people unhappy. Consumer groups felt the FDA had left the public open to carcinogenic sweeteners; the diet drink and food industry wailed over the loss of profits from the billion-dollar-a-year business; and the public was split between its desire to get thin and its relief in having one less source of carcinogens to cope with.

It was left to the U.S. Senate to keep the FDA's negative balance intact; the Senate in mid-September, 1977, voted, 87 to 7, not to insist on cancer warnings in saccharin ads. This action called for a meeting with a House committee and an 18-month delay in further studies. Once again, the FDA was saved from performing a useful function.

Meanwhile, the public was left to the sugar addiction which had rotted its teeth from infancy and had been incorpo-

rated into its canned, packaged and prepared and otherwise processed foods in concentrations which fattened people, promoted diabetes and induced many other disabilities and infirmities.

One could not prevail over the saccharin lobby. Nor the sugar lobby. Nor any of the lobbies which could pay the price for congressional legislation or buy bureaucrats, or rent other functions of a government "of, by and for the people."

There were times when the FDA could be brutally candid about the perils of eating food and using medicines in the United States. This was usually true when the agency was dramatizing the need for its services and asking for more money or authority.

Harold M. Schmeck of the *New York Times* wrote in 1976 about an upcoming revision of food and drug laws to end fraud in reporting the results of animal tests. The violations could—but never did—result in criminal prosecution.

Schmeck quoted the FDA commissioner, Dr. Alexander M. Schmidt, as complaining, "Recent FDA investigations have found animal studies poorly carried out and data which were improperly reported or not reported at all.".

An FDA analysis of the situation gave several examples of experiments which were "poorly conceived, carelessly executed or inaccurately analyzed or reported." Among them were these: When tissue specimens were examined by several scientists, each of whom reached different conclusions, only the conclusions favorable to the product reached the FDA; and "Animals were recorded as normal for a variety of factors, including appearance, awareness, appetite and thirst, when in fact, the animals were dead."

A few months after the FDA announcement, a federal Review Panel on New Drug Regulation, which for two years had been investigating the FDA's operations, agreed with charges of sloppy reporting and fraud by scientists and drug houses; but the independent panel blamed the FDA for permitting the practices. The panel admonished that "research-

ers and drug sponsors must believe that sanctions will be imposed on those who submit inaccurate or misleading information.'' While making it clear it had not found the FDA to be a tool of the drug industry, as some had charged, the panel said the FDA should keep the industry's representatives off its advisory review boards, and put more consumer representatives on them.

The panel's substantive charges amounted pretty much to a list of criticisms that committees and commissions and the man on the streets of Washington had been making for years: Despite a river of news and self-serving releases flowing from the FDA's publicity staff, the tax-paying public was kept in ignorance of important FDA dealings with industry; the agency's scientific setup was bad and getting worse; the drug regulatory system enacted by Congress in 1962 is fundamentally sound, but the FDA is inefficient in reviewing applications for new drug approval.

The 400-page report, put together by the panel's seven members and a staff of 54 persons over 27 months, moved into a higher gear when Joseph A. Califano, Jr., Secretary of Health, Education and Welfare, endorsed it and said that the basic drug law needed a thorough overhaul.

Califano said that in 40 years drug sales rose from $300 million a year to more than $7 billion, with $1.5 billion being paid for with federal Medicare and Medicaid money. He said that doctors were writing a total of 1.5 billion prescriptions a year, an average of 5.7 for every man, woman and child in the United States. To point up the need for more accurate accounting, he cited the fact that the FDA's system of voluntary reporting by doctors of 10,000 to 12,000 adverse reactions to drugs annually contrasted with the 6 million estimated in 1974 by the General Accounting Office. He left the impression that new food and drug laws would make regulatory standards more flexible, give the public a role in approving new drugs and sharpen the reporting of toxic reactions.

Senator Edward M. Kennedy, a longtime critic of the FDA

and chairman of a subcommittee which had investigated the agency, predicted that the present laws would be rewritten. "A task that is long overdue," he added.

To many who had followed the fortunes of the FDA over four decades it seemed that at long last the agency would be forced to adopt a modicum of efficiency. But there remained the memory of numerous other committees, commissions and politicians who had made similar utterances down through time. And there was the uneasy feeling of truth in a well-worn saying that reorganization of the FDA is like musical chairs: the same old names and faces turn up with new titles and behind new desks.

Considering the internal affairs of the FDA, it is easy to understand why the list of recent commissioners is so long and their terms in office so short. There were five commissioners between 1966 and 1977.

The FDA has perfected a neat disciplinary device for censoring and silencing drug manufacturers and scientists, thus enabling the agency to take its own time in acting on new drug applications without being publicly exposed by abused people. In its instruction called *Clinical Testing for Safe and Effective Drugs*, the FDA warns: "The regulations forbid manufacturers or any persons acting for or on their behalf to disseminate any promotional material concerning a new drug prior to completion of the investigation." The document hastens to add that "this is not intended to restrict the full exchange of scientific findings in scientific or other communications media." It is entirely up to the FDA to determine what constitutes a violation, which scientists will be denied further supplies of the drug, and which manufacturers will lose their right to sponsor investigations. Under this ukase, any scientist addressing his peers at a professional meeting could be punished if a journalist reported his remarks about a drug being tested.

Stanley Jacob first ran afoul of FDA rules in 1963 when a contract was filed in the Oregon state capital, Salem, awarding DMSO patent rights jointly to the University of Oregon and Crown Zellerbach. Inasmuch as the filed contract became a public document, reporters naturally wrote up the medical uses claimed for DMSO. Neither Jacob nor any party to the contract, nor even the FDA, had the power to stop

publication. The FDA never seemed able to understand this; and to this day the agency, some of its officials and even scattered scientists (who should know better) blame Jacob for prematurely "going public."

Stanley Jacob was taught a lesson by the FDA, but it is doubtful that he learned it well. He continued to confront his persecutors quietly, firmly. When the FDA punished not only himself but millions of sick and disabled people who stood to benefit by DMSO therapy, he spoke out. In one sense, Stanley Jacob lost many battles with the FDA; for twelve long years the agency denied him, other physicians, and the people free access to DMSO.

In another sense, Jacob is the victor; most of his persecutors have left the FDA, or been drummed out of it, to claim jobs from the food and drug companies they supposedly had regulated. Jacob still fought a long, hard war but a winning one. For some, it may be difficult to believe that officers of the United States Government could stoop to the vengeful tactics pursued by the FDA. From my own experience, I have no doubt about it.

Crown Zellerbach also was taught a lesson, and the corporation and its officers learned it well. The lesson was to keep their mouths shut on matters involving the FDA. CZ has lived in a state of panic from the day the FDA first raided their precincts until this writing.

The FDA's critics and their criticisms and the FDA's alibis have been many and varied. Here is a random sampling;

*The General Accounting Office, which disclosed "alarming adverse reactions to new drugs," including the death of eight soldiers in an Army test of an anti-malarial, proposed that the FDA take legal action to force compliance by pharmaceutical houses, doctors and scientists with the law. The Department of Health, Education and Welfare reacted negatively, for one reason, because a "hostile FDA might produce a reluctance to cooperate with the agency, or worse, a disincentive for research itself."

*FDA Commissioner Alexander Schmidt, who resigned in 1977, explained to a Senate committee on health why the agency was generally so negative toward new drugs—an attitude that costs drug makers many millions of dollars and a decade or more of time to gain approval for a new preparation. He said that when a controversial drug is approved, the FDA, the drug house and the individuals involved are closely investigated by Congress, while no inquiry is made when the FDA rejects a drug application. Said Schmidt: "The Congressional pressure for negative action is, therefore, intense and ever increasing."

The answer, like that of so many more by agency VIP's, tended to minimize the agency's responsibility for its poor performance. The blame rested with Congress.

*An outside Review Panel on New Drug Regulation investigated charges that staff members had been harassed by FDA officials and the recurrent complaint that drug houses dominated the FDA. The panel recommended reprimands for five past and present FDA VIP's and apologies to a dozen hounded medical officers. The way the FDA explained it: "Beginning in 1970, FDA management, while not dominated by industry, made a conscious effort to make the agency less adversarial towards and more cooperative with drug manufacturers and to neutralize reviewing medical officers who followed a different philosophy."

*Schmidt once decided to investigate personally reports by 14 present and past FDA officials that the FDA was being manipulated by the drug industry. One year and 909 pages of report later, he announced that he had found no evidence to support charges of improper drug approvals, bias in favor of approving drugs, industry domination of the FDA, harassment of employees, deliberate misuse of advisory committees, secret policy meetings or attempts to change agency documents. According to the Associated Press, Schmidt explained it all away: "Like most organizations, large or small, FDA has serious internal problems in communicating." Senator Edward M. Kennedy was less than enthusiastic about Schmidt's vindication of FDA. Kennedy said, "The report does not remove doubts of his agency's capability to protect the health and safety of the American people."

*The General Accounting Office complained to a House Commerce subcommitte investigating conflict of interest among federal regulatory agency employees that about 150 FDA officials were holding stock in food, drug,

cosmetic and other companies that the FDA regulated, 27 of them undetected by the FDA. Of 61 instructed to divest themselves of their stock, 30 complied, 14 asked for an exception or an extension of time. And an additional 17 did not respond. The FDA explained that its conflict-of-interest regulations exceed requirements of the statute "and are more comprehensive than those of other agencies and vigilantly enforced."

*Another Congressional investigation found that more than one half (24 of 45) the people appointed to nine regulatory agencies, including the FDA, between 1970 and 1975 came from the industries they now were to regulate. And of 120 appointed regulators appointed during the last 15 years, 27 had been practicing law before the commissions they joined, and 20 more had been congressmen or congressional aides.

Victor H. Kramer, the Georgetown University law professor who headed the investigation, said, "Partisan political considerations dominate the selection of regulators to an alarming extent—alarming in that other factors, such as competence, experience and even, on occasion, regulatory philosophy, are only secondary factors."

Over the years, several presidents and numerous congressional committees have vowed to reorganize the FDA—admittedly a job of Herculean stature—but, so far, the bureau has proved as immutable as the sphinx.

When one looks specifically at the FDA's treatment of DMSO, several questions arise: Was there no one to protect consumers against the high-handed deportment of the FDA? Was there no one to cry out against bureaucracy's sacrifice of God-knows-how-many lives when a potential remedy for some lethal illnesses and scores of disabling conditions was at hand? Was there no responsible arm of government to intervene? No voluntary health agency to demand a halt to the abuse of sick citizens? No press—no newspapers, no radio, no television—to expose one of the shabbiest episodes in the nation's history of governmental mismanagement? Where were the consumers' advocates? Was there no lobby, no political group, no industrial or financial interest to exert pressure on the wayward agency?

Few expected much support for DMSO from the scientific and medical journals, which by and large hew to safe and respectable orthodoxy and eschew bold new approaches to old problems. Some of the most significant scientific papers of this century finally found publication after having been rejected more often than the manuscript of *Gone With the Wind*.

There *were* protests—protests galore from patients on DMSO who suddenly found they were forbidden access to the one preparation that controlled their pains, healed their hurts, sometimes even reversed the chronic conditions which

would lead to untimely death. Some physicians of considerable stature and a few journal editors complained that a heartless, mindless government bureau was usurping doctors' rights and was consigning their patients to disability and death. These protests, however, were sparse, amateurish, and unheard over the thunderous silence of the FDA and the din of a hundred other complaints about the agency's numerous shortcomings.

Where were the pros? The politicians posed for pictures, uttered the proper statements which got their names in the news, and with a few notable exceptions, let it go at that. The pharmaceutical industry noted the banning of DMSO with quiet resignation; with the cheap "wonder drug" ruled off the market, major houses were rid of a superior product which might well compete with their expensive wares.

While some small consumer agencies tried valiantly to spread the story of DMSO's suppression, the potent ones remained silent; Ralph Nader and his raiders were so preoccupied with the noxious substances the FDA allowed in food and drugs that they failed to consider the FDA's other mortal sin—withholding beneficial drugs. The hard-hitting TV show, *60 Minutes*, prepared an episode on DMSO—and dropped it.

Metropolitan news media—newspapers, television and radio—usually assign special writers to cover matters in the field of health. These science writers are familiar with the medical mystique and can discuss glibly the synthesis of DNA and RNA, the new virus around town and the latest bypass operation to avoid heart attacks. They call famous doctors by their first names. The doctors, the administrators of the great medical centers, fund raisers, and the skilled public relations staffs help the writers; they define quackery and privately identify quacks (quite often as anyone without due reverence for The Establishment or with a new idea for controlling cancer). They also give valuable awards for medical writing and supply the writers with interviews, press

releases, data, or a friendly lunch or a drink. The writers are inducted into this close camaraderie of medical and scientific societies, government granting agencies, great research and hospital facilities, voluntary health associations, commercial lobbies, and a glittering circle of social, industrial and financial giants who serve as directors and backers of the major health institutions and movements. This conglomerate sometimes is referred to as The Establishment; and its adherents and members often speak as with one voice, almost invariably a conservative voice, a negative voice.

Too often, science and medical writers identify Establishment fuddy duddies as "authorities," "high officials," "informed sources," or by some other complimentary term; frequently, they ignore or minimize contrary views. In this servile, or symbiotic, relationship, the media, perhaps unwittingly, become the propaganda arm of The Establishment.

It is fortunate that some writers—and, indeed, a few rebels within The Establishment, and the hell-raising insurgents within the FDA itself—seek the facts for themselves and judge evidence on its merits rather than on the bias of Establishment gurus. These dissenters make progress possible by non-Establishmentarian geniuses and stand guard over the soul of science. By so doing, they pay a price—sometimes a heavy price in the loss of some or all access to "respectable" news sources.

In the ecology of the news world, the newsperson and the news sources quite naturally form a mutual bond of sympathy, a reciprocity of protection, a continuing exchange of favors, the kind of ties human beings find it hard to sever, even for journalistic enterprise and truth. Too few journalists are prepared to make the sacrifices necessary to end FDA abuses of the public's health needs.

America is a health-conscious nation and is becoming more so with every passing year. One measure of our efforts to be healthy lies in the amount we invest through the federal government. A 1977 book, *The Federal Health Dollar, 1969–1976,* published by the National Planning Association's Center for Health Policy Studies, stated that, at an ever-accelerating rate, the federal funds for health care zoomed in seven years from $16.7 to $42.4 billion—a growth rate of more than 250 per cent.

What does the citizenry get for this stupendous outlay? It has both a bureaucracy of questionable merit, which, some feel, does more harm than good to the health of the nation. If the FDA were representative of the health agencies (and I feel that would be an unfair generalization) we undoubtedly would be well advised to scrap all government health agencies and probably most of the non-governmental agencies as well. Private enterprise could do no worse than the present Health Establishment, which has deprived most Americans of decent care. By virtue of its authoritative power to punish or protect and dispense billions of dollars to those who will go along quietly with the system, The Establishment dominates the behavior and thinking of most physicians and scientists.

The Establishment, a loose association of federal, state and local agencies, medical and scientific professional

groups, and the big money-raising voluntary outfits, is the promoter of outmoded medical procedures, the protector of those whose doors and minds are closed against innovative life-saving processes.

DMSO was not the only victim of the FDA's indolent behavior. Almost all new drugs got "the treatment," although DMSO seemed to get a double dose of it. The reason for this probably was that it would be embarrassing for the FDA and those who had lied about DMSO for so many years to eat their words.

Sodium valporate is a case in point. This drug, regarded as affording epileptics dramatic relief from seizures, had been in use in numerous other countries for up to almost a decade, when the FDA saw fit to defend itself in a general news release issued in mid-1977. The agency complained, "Melodramatic stories of epileptics being forced to go abroad to obtain sodium valporate appear increasingly popular with some segments of the press."

The FDA, caught at last, said it would issue what it called "compassionate IND's" to physicians applying for permission to prescribe it. It blamed the American drug house (Abbott) for the delay, saying it had failed so far to present its case for approval. "The FDA cannot force any private company to provide any given drug to the American market," the release said. This excuse had a familiar ring.

A month later, the FDA approved Tagamet for Smith Kline Corporation, and thus made this drug available to the four million Americans with duodenal ulcers and other diseases due to hypersecretion of the stomach's acid-producing cells. Smith Kline had conducted its research and released the drug first in the United Kingdom, well beyond the FDA's authority to halt clinical trials or deny its marketing.

At about the same time, the FDA's high walls were finally breached to permit the licensing in the United States of several other drugs of merit demonstrated in trials abroad.

In its round-up of important events during 1977, the American Medical Association, which has little trouble restraining its enthusiasms, stated, "Perhaps the most important medical development of the year 1977 came at the year's end, with government licensing of a new vaccine to prevent one common form of pneumonia that kills about 25,000 Americans each year." The drug was tested in South Africa.

The AMA stated, as another item, "Asthma sufferers were benefiting in the fall from two new drugs which have been available in Europe for many years." The drugs were beclomethasone dipropionate and cromolyn sodium.

The AMA, perhaps to balance its report, exercised its clout against liquid protein, "the fad diet of the year;" and laetrile, an anti-cancer drug which is presumably safe but which "all leading scientific organizations, including the AMA, declared worthless against cancer."

The AMA warned dolefully, "The lid is off," in describing one of the great consumer victories of the year. The FDA's long fight to impose severe restrictions on the free sale of vitamins A and D had been beaten down decisively in Congress and in the courts. This defeat of its old food supplement fetish may have been a major factor in inducing the FDA to relax other stern interdictions which for many years had deprived the sick and dying of the benefits of new drugs. In ruling against the FDA, the U.S. Court of Appeals stated: "The regulation is invalid as arbitrary and capricious and not in accordance with the law."

Some uncharitable FDA-watchers speculated that the new mood toward releasing drugs was due not so much to the agency's contrite decision to ease up on its abuse of sick people as it was due to bureaucrats' desire to preserve their jobs and salvage their powers. The FDA had come under attack from many quarters; consumer groups, medical organizations, the press and finally, the real crusher, the courts and state governments which were challenging the agency on the grounds of state's rights. A federal judge in Oklahoma

City ruled that a physician might give his terminal cancer patient the controversial drug, laetrile; another judge in Brooklyn did likewise. Some were demanding that the FDA be broken up.

The legislatures of Florida and Oregon passed bills making it legal for doctors to prescribe DMSO for their patients; but the Governor of Florida vetoed the bill, and Oregonians learned that, since DMSO was not produced in that state, the only way to make it available would be to smuggle in it—a challenge to federal law that never was issued. The only plant producing DMSO in the United States was located in Bogaloosa, La.; ironically, it was owned and operated by Crown Zellerbach, whose main forests were in the Pacific Northwest.

Despite the failure to effect the release of DMSO within their precincts, the states of Florida and Oregon made it possible for many physicians to prescribe DMSO for a host of patients.

The long and fervently hoped for change in the federal regulations governing food and drugs appeared to be in the offing early in 1978. The *Wall Street Journal* of December 12, 1977, had carried a story outlining what it called the draft of a new law to be proposed by the Carter Administration which "basically would make it faster and easier for the FDA to approve the marketing of new drugs and to pull problem drugs off the shelves."

The draft provided for: cutting the lag between applications to market a product and FDA approval; controlled distribution of a drug while testing it; quicker approval and well controlled clinical use of "breakthrough" drugs, especially if they are the best available for life-threatening or seriously disabling conditions; dropping the requirement that a drug company give the FDA its own data proving safety and efficacy, even when another company already has supplied the information; removal of drugs from the market if they pose a "significant risk of serious illness or injury" instead of the former wording, present an "imminent hazard;" companies to monitor the effects of new drugs on the market and turn the data over to the FDA; removal of restrictions against publishing new-drug test data at the time of application (instead of, as now, time of approval); and a label on all non-prescriptive and most prescribed drugs, giving dosage information and a caution against side effects.

These provisions looked good, although it was hard to see how some of the improvements would be effected. Three others could contain traps: 1) increased enforcement powers, including subpoena, and, for violations of drug laws, civil fines of up to $10,000 a day, as well as criminal penalities; 2) a single set of ground rules for handling all applications, thus "slashing red tape;" and 3) halting the export of drugs to foreign countries without FDA approval.

Skeptics, mindful of FDA's subjective use of its police powers in the past, the suspicions of the sale of its favors to drug houses, and the possibility of imposing upon other countries the arrogance it exercised at home, had reservations. They questioned the wisdom of changing the regulations without at the same time substituting new people with new ideas and old-fashioned concepts of morality and ethics for the kingpins of the old bureaucracy. Some felt the changes would amount to no more than another round of musical chairs, the same old wincing up behind new desks.

And some viewed, as in a hideous nightmare, reports that duties having to do with food, drugs, cosmetics and medical devices would be shifted from several other agencies and placed under a greatly expanded FDA.

The dawn of 1978 was not an entirely rosy one.

We live dangerously. Moreover, life is getting riskier all the time.

Perils lurk in the air we breathe, the water we drink, the foods we eat, the cosmetics we use, the drugs we take, the devices we use and the implements used on us.

The dangers lie in chemicals with long, difficult-to-pronounce names or such acronyms as DDT, PCB, PBB, DBCP, TCE, DES and DNA. The toxins are used variously as pesticides, animal fatteners, fire retardants, baby baths, soft drink containers, food and hair dyes, birth control pills, tranquilizers, industrial products, human reducing agents and for many other purposes.

High hazards exist not only in drugs but in other aspects of medical treatment as well. Medical and dental x-rays for diagnosis and treatment are examples. And, of course, many habits, like drinking and smoking, place people in jeopardy.

All in all, these dangers have been shown to have such varied effects as nerve disorders leading to paralysis, leukemia and other cancers, heart and circulatory diseases, miscarriages, birth defects, drug addiction and death.

Now come new threats involving both the microcosm and the macrocosm. Gene splicing, or efforts to mate different strains of DNA and thus synthesize new life forms, including viruses and germs with which our immune systems are unable to cope, could bring on a plague the likes of which the

animal and plant world have never experienced. On the other hand, we are told that the broad use of fluorocarbon propellant containers could impair the world's ozone layer which protects us from outer space radiation. Skin cancers for all!

My point is we do need federal bureaus to protect us from these menaces. Despite the impression of bustle that the FDA's able publicity staff lends to the agency in its bales of press releases, the FDA by its accomplishments—or, rather, lack of accomplishments—has shown it is not up to any of the jobs it is supposed to do.

During the years following the FDA's shackling of DMSO, there has been no new evidence—or, indeed, any old or overlooked evidence—of toxicity. True, the FDA did finance a sort of review of the status of DMSO by a special committee of the National Academy of Sciences. The committee report virtually parroted the tired and discredited contentions of its sponsor, the FDA. Following this there was a long, embarrassed silence during which thoughtful observers may have marveled at the ease and economy with which a committee of the nation's most prestigious scientific body could be influenced. The success in controlling the minds of the distinguished panelists must compare favorably with the best CIA experiments in programming human behavior. Subsequently, no responsible official or scientist seems to have attributed toxicity to DMSO.

I once reminded a medical doctor, the government official in charge of the DMSO matter, of the FDA's earlier alarums about the drug; their equating DMSO with thalidomide, the teratogenic sleeping potion, and their "DMSO-will-make-you-blind" bit. He answered that "we have stopped saying things like that." Nevertheless, more years passed before meaningful research with DMSO was permitted.

So far as I have been able to learn, there still is no scientific evidence to contradict the statements of many hundreds of scientists who have reported that DMSO, alone or in combi-

nation with other drugs, has produced modest to spectacular benefit in scores of illnesses. With gratifying frequency, DMSO has yielded complete remissions in such often-serious pathology as arthritis (osteo-rhematoid and gout), thrombophlebitis, bursitis, burns, scars, trauma (sprains, strains, whiplash), mouth troubles (toothaches, gingivitis, gum problems), nose and throat inflammations, inner ear pains, radiation burns, and viral, fungal and bacterial infections. The earlier DMSO is applied the more dramatic its effect.

There were other DMSO indications as well which had been discussed at scientific meetings, recorded in journals and even outlined in large drug houses' memoranda as a forerunner to DMSO's once imminent release as a prescription drug, just before the FDA banned it.

Other leads too were discouraged when the FDA clamped down on testing. Some of them stemmed from observations of DMSO's effects in laboratory dishes; its selective destruction of leukemic cells, for instance . . . or its prevention of death from heart attacks induced in experimental animals.

Several years after the ban, the FDA permitted the use of DMSO in veterinary medicine for the dog's inflamed anus and the horse's stiff or injured joints. Tests of other reported benefits of DMSO in animals—hoof and mouth disease, mastitis, foot rot, edema and lumbago, to name a few—were not permitted by the FDA order. Pain-tortured humans fortunate enough to know a friendly veterinarian bought bootleg DMSO and, to this extent, became as privileged as horses and dogs.

The acme (or the nadir) of the FDA's authority lay in the indiscriminate ban's not affording DMSO's favors to plants. Crop reports showed that DMSO sprays had increased yields from 10 to 25 per cent, and by incorporating an antibiotic or another preparation, had prevented pestilential devastation.

The thalidomide shibboleth extended the FDA's influence worldwide; the agency's punitive authority over research,

however, was still limited to the United States. As time passed, Italians began using DMSO on athletic injuries; Mexicans were showing it useful in arthritis and neuralgia; laboratories in Berlin incorporated it in typhus vaccines; in Heidelberg, it was employed against benign breast disease; scientists in the Soviet Union were intrigued with its activity against fungal infections; the Swiss were impressed by its blessings in scleroderma, in arterial occulsion and in post-thrombotic disease.

In a curious reversal of roles, the survival abroad of human rights to enlightened medical care gave hope that the same freedom someday might be rekindled in America to stem a retreat to the science and medicine of the Middle Ages.

Dr. Chauncey D. Leake, of the University of California Medical Center in San Francisco, a wise and courageous leader in the field of medical education, in opening the third international conference on DMSO on January 17, 1975, said that the FDA operates under an act "which seems to imply that no drug is to be used by a physician unless it is demonstrated to be absolutely safe and absolutely effective."

"There is no such drug," he added. "Not even tap water or table salt is absolutely safe and effective."

He stated that it is the responsibility of government and the pharmaceutical industry to furnish the scientific facts about a drug: what it is, what it does, when it should be used or not used and details of its dosages, reactions in cells and effect upon tissues and systems.

"Then it is up to the judgment of licensed physicians to decide how and for what purpose they will use it."

In these simple statements of fact, Leake, a giant in science and medicine, summed up a basic situation which bureaucracy had complicated beyond all understanding. He spoke to an attentive audience of physicians and scientists who had used DMSO and now came together under the aegis of the New York Academy of Sciences to compare notes.

The researchers were virtually unanimous in finding

DMSO helpful in a host of disease conditions; and uniformly they reported it to have negligible, if any, toxicity.

A dozen years have passed since the FDA banished DMSO from clinical and experimental use as a drug. In that interval countless millions of people have died of causes for which DMSO was a treatment. No one will ever know how many of these patients died unnecessarily or became paralyzed and bedridden, when DMSO might have helped them.

DMSO is recognized now by those current with the situation—including honest top echelon FDA officers who have followed the fate of the drug—as being non-toxic. Inasmuch as there is not one scintilla of scientific evidence that DMSO has ever harmed a human being seriously (its common side effects are a brief rash and a garlicky odor), it may well be the safest drug every widely used. But your family doctor has learned well the lesson taught by the FDA a decade and more ago; and if you ask him, he is likely to advise you that "DMSO can make you blind." The FDA has never recanted nor atoned in public for its untruths.

Despite the strictures, DMSO research continues. When scientists abroad finally found out that the FDA alarums were unwarranted and that the FDA was not to be trusted, they went ahead with their clinical experiments and at this writing DMSO has been a prescriptive drug for one or more indications in the Soviet Union (since April, 1971), West Germany, Austria, Switzerland (with IDU for shingles and other virus diseases), Canada (for scleroderma), Great Britain and Ireland (with IDU, for shingles and other Herpes virus conditions, including a blinding eye infection, cold sores, and what has become a raging venereal epidemic), in China (for psoriasis), in several research centers in South America and elsewhere for numerous other conditions, many of which are discussed in this book.

In recent years, a few bold souls in the United States have won the right to test DMSO in about a dozen research centers on clinical conditions such as interstitial cystitis and

scleroderma and a few others which can not be treated satisfactorily otherwise. Only a few of the United States projects have reached the stage where sick and disabled human subjects are treated; other experiments permitted by the FDA involve noting how cells growing in test tubes react to DMSO and the effect of the drug on animals, naturally ill or made ill by various means.

There are areas of suppressed excitement in DMSO research. Preliminary advances hold promise of new controls over the toll of the four leading killers—heart disease, cancer, stroke and accidents—which account for about 70 per cent of all deaths in the United States. A DMSO rub-on vaccine may achieve a new dimension in the control of presently incurable infections and benign and malignant tumors. DMSO-treated animals have been enabled to survive a bullet in the brain, and so may humans.

Perhaps the liveliest promise for the early testing of these and other new disease controls lies in the shakiness of the structure of the FDA, the arrogant, bumbling bureau which has done irreparable harm to the health of the people. The first rebellions have broken out among the citizenry and state governments, and these eventually could lead to rewinning long lost freedoms, including the right to the best possible treatment for disease.

Confidence has been shaken not only in the Government's management of health matters but also in the practice of medicine and conventions of science. When one applies DMSO to a fresh black eye or other bruise and sees the ugly discoloration and swelling disappear within minutes, one tends to lose faith in the caveats of practitioners of conservative medicine. When one swabs a little DMSO on a fresh burn and stops the pain instantly and notes rapid healing without scarring, all the double-blind tests in the world, together with their often-rigged statistics and naive conclusions, couldn't persuade one that it is wrong to treat oneself with DMSO.

APPENDIX:
A Sampling of research done on DMSO

ARTHRITIS

Salvador Chavarria, M.D., was a Houston rheumatologist who not only had noted and recorded DMSO's effects in his numerous patients but also drew handsome fees for his diagnostic and therapeutic services in prescribing it for the many indications for which it was honored prior to the FDA crackdown.

When the local medical societies, of which he was a member in good standing, began making hostile noises for his use of an FDA-cursed preparation, Chavarria moved his practice business across the border into a Mexican town called Piedras Negras, in the State of Coahuila.

Betty Lee Morales visited Piedras Negras and wrote her observations in the December, 1977, issue of the magazine, *Let's Live*, under the title "Arthritis: A Three Day Cure." She wrote that Chavarria discovered that DMSO in a glucose solution was safe as an intravenous injection and soon found himself swamped with appointments. "Good news travels fast," she wrote, "like one patient telling another that after the first two-hour trip she was miraculously free of all pain; joints loosened up; fingers unlocked; knees became flexible; back pains vanished."

Morales interviewed Americans from a dozen or more states the day she visited Charvarria's Clinica de Especialis-

tas, S.A.; and she described the diagnostic work-up and treatment they had undergone. All patients declared they had improved greatly, some of them remarkably. She reported that besides all three major arthritides—gout, rheumatoid and osteoarthritis—other joint pains were responding well in such conditions as scleroderma, sciatica, muscle spasms and spondilitis, tubercular and other vertebral inflammations and lupus erythematosis.

ATHLETIC INJURIES

A total of 47 athletes were treated for sports-associated conditions—30 of them with acute sprains, strains, dislocations, serious cuts and the like, 7 of them with the syndromes which follow long immobilization for broken bones, and 10 for tennis elbow and other chronic conditions considered the result of a long series of "microtraumas." A wide range of sports were included—gymnastics, track and field events, Greco-Roman and conventional wrestling, football, tennis, basketball, judo, diving, swimming, weight-lifting, skiing, cycling, water polo and fencing.

The patients were treated three times a day for two days and twice a day thereafter by dabbing or pouring 90 per cent DMSO on the affected areas.

In cases of acute trauma, pain was relieved rapidly, sometimes spectacularly, swelling subsided, and function was recovered—"so spectacularly as to compel us to urge our patients to observe greatest caution in order to avoid further damage to a joint" which may not have healed completely.

Chronic conditions, some of which had become acute again, also responded rapidly with relief of pain, reduced swelling and increased function. DMSO also promoted rapid recovery and return to action following immobilization for fractures.

"The complete absence of undesirable collateral reac-

tions, its ease of applications, and the few precautions that should be observed make it (DMSO) a medication for wide use in medical therapy, and also an urgently needed medication in sports-related traumatology." [A. Venerando et al., Institute of Sports Medicine, Italy, *Gazz. Int. Med. Chir.* 70:1605 (1965)]

PAIN

DMSO, alone and in combination with hydrocortisone, novocain or edan, was applied to the skin overlying painful areas in 76 patients with diseases of rheumatoid origin, inflammation of nerve roots or spinal disc problems. For experimental patients, 85 per cent DMSO was used; in control patients, 1 per cent DMSO.

As compared with control patients, those treated with 85 per cent DMSO began showing improvement as early as one hour after treatment, with the greatest improvement after three hours. In some cases pain disappeared completely. Within one week of treatment improvement was recorded for 5 of the 8 rheumatoid patients, 17 of 20 cases of inflammation of nerve roots, and 8 of 10 people with disc pains.

All DMSO treatments were superior to conventional therapy. DMSO was most effective when given with hydrocortisone, novocain or edan. [Jacek Glazewski, Tarnow, *Polish Literature*]

WOUND HEALING

Rabbits were anesthetized and surgical wounds were inflicted along the backs. Some wounds were swabbed immediately and periodically thereafter with 70 per cent DMSO. All wounds then were sutured and the animals put in isolation. Sutures were removed on the fourth day, and the

animals were killed and autopsied between then and the fourteenth day.

Scar tissue was removed and measured for its ability to withstand tension without rupturing.

No differences were observed in tissues of animals killed before the seventh day. Those killed from then on however registered striking differences: The scar tissue of the DMSO-treated rabbits was "very significantly" (one chance of error in 100) the stronger, possibly due to an increased blood supply to the superficial tissues. [Harold M. Albert of New Orleans and Nguyen Huu of Saigon, *La Presse Medicale*, January 7, 1967]

PLASTIC SURGERY

Skin grafts, even with tissue removed from one side and transplanted to another site on the same body, often fail. Evidently, proteolytic enzymes become active and destroy the graft moorings.

Dressings moistened with 30 per cent DMSO solution enabled grafts to take and survive in badly burned patients and victims of elephantiasis. [M.F. Kamaev, Lvov Medical Institute; *Klin Khir* (Kiev), 5 (1969): 65–67)]

EAR TROUBLE

A simple procedure was tested successfully in 69 patients, 37 girls and 32 boys, with otitis media, or inflammation of the middle ear, and 17 with inflammation of the maxillary sinus.

A 30–50 per cent solution of DMSO was poured into the cleaned ear and put under slight pressure. The solution, sometimes containing an antibiotic, usually penetrated to the eustachian tube, bathed it, and passed out into the

nasopharynx. In suppurative otitis media, there was rapid cessation of suppuration, or pus discharge, return of hearing and normalization of the blood.

In purulent inflammation of the antrums of Highmore, 30–50 per cent DMSO was given by puncture. Cures were achieved in a majority of cases within 4–8 days; and the results of treatment usually were long-lasting. [Ia. M. Golod, Soviet Union, *Zhurnal Ushnykh, Nosovykh i Gorlovykh Boleznei*, 4, (1969): 65–66]

EAR SURGERY

A simple but painful operation is puncturing the eardrum to release pus and pressure from the inner or middle ear and introduce medicines to combat infection or other disease conditions. Some doctors elect to let their patients suffer the lesser pains of otitis rather than subject them to the pain of operation.

DMSO solved the problem in 107 patients with serous otitis and 50 with purulent otitis media. A single drop of DMSO was swabbed on the eardrums for one minute; it and an anesthetic, tetracaine hydrochlorida, made it possible to puncture the eardrum. None of the patients had severe pain; four out of five had no pain at all, and the rest slight pain. [Irving L. Ochs, of Annapolis, Md., at American Academy of Ophthalmology and Otolaryngology annual meeting, 1966]

PERIODONTAL DISEASE

A total of 32 men and women 18 to 45 years old with periodontal disease were treated with DMSO.

In 13, the disease appeared restricted to bleeding and swollen superficial layers of the gums. In the other 19,

oozing and painful pockets of infection extended deep into the gums, sometimes involving bone and loosening teeth.

Following diagnostic x-rays, teeth cleaning and repair, microscopic examination of gum samples, blood and fluid tests to identify germs and other sources of disease, the patients were treated with compresses containing 30 per cent DMSO applied to the outside of the gums for ten minutes during each of seven to ten visits on alternate days. Twenty non-diseased people, as controls, were similarly treated.

"Remarkable improvement"—total elimination of pain, decreased bleeding, and gum adherence to teeth—occurred in all patients with superficial disease. All patients with deep infections reported less inflammation and disappearance of painful symptoms, but in none did very loose teeth firm up. Controls experienced no untoward reactions. [Prof. Dr. J. Krzywicki, Head of the Clinic of Behavioral Stomatology Medical Academy, Warsaw, Poland, *Czas Stomat* XXII:LL (1969): 1007–10]

TEETH

Researchers at the University of Bern conducted controlled studies of pulpitis treatments for ten years. Pulpitis is inflammation of the central part of teeth, the part containing the nerve and blood vessels.

DMSO alone improved 75 per cent of the cases; and DMSO plus oxyphenylbutazone (a drug for gout) or chloramphenicol improved 85 per cent, as compared with 50 per cent of those on placebos. [H. Triadan, *Medicine and Hygiene*, 826 bis/May 22, 1968]

FUNGUS INFECTION

A patient with an infection of the foot by M apiospermum which was unresponsive to antifungal agents rejected ampu-

tation. He was treated through an indwelling catheter to the infected area two hours a day for 16 days with amphotericin B (and later Fenticlor) dissolved in 60 per cent DMSO. The patient improved and was discharged; no serious side effects were noted.

Four months later, the patient was treated for a recurrence, which was found due to a complicating bacterial infection. The leg was amputated; and examination and tests showed no fungi present. [C. Edward Buckley III, et al., Duke Univ. Med. Center, *Arch. Intern. Med.*, December 1969]

RINGWORM

The antibiotic, griseofulvin, will not cure ringworm, and DMSO alone will not cure ringworm.

But a paste of griseofulvin tablets in DMSO cleared it up completely in 5–10 days in cats. [H.B. Levine et al., Naval Biomedical Research Laboratory, Univ. of Calif. School of Public Health, *Sabouraudia* 9(1971):43–49]

PSORIASIS

Drs. Chiao Ching-jung and Li Hsi-shun of the Lanchow General Hospital of the Chinese People's Liberation Army reported in the Chinese Medical Journal of September, 1973, that they gave 33 patients severely ill with psoriasis an extract of camptotheca nuts dissolved in DMSO. The procedure turned out to be a "quick, effective and convenient treatment," they said.

When they totted up the score the following year, the physicians found that after a few weeks treatment, 21 cases had resulted in a "clinical cure;" that is, all eruptions had subsided, the pimples had been replaced by normal skin, and the scales had disappeared. All 12 remaining patients had "greatly improved;" a few eruptions still could be found

along with discolored patches of skin (especially on the lower legs) which showed where the lesions had been.

Camptotheca herbs had been used in China since 1971 to treat cancer; the extracts killed some of the cancers, but, unless they were administered with extreme care, they also tended to kill the patients. Dissolved in 70 per cent DMSO, the 3—5 percent camptothecine extracts were simply swabbed on the skin. Within five minutes, the patient usually felt an itching, stinging or burning pain, which subsided in another five or ten minutes. Within three days, the slight rash at the site of application subsided and the pimples began to shrivel up and disappear. Most skin eruptions were gone in two or three weeks.

In some cases, the researchers applied the camptothecine/DMSO ointment to only one side of the patient's body. The psoriatic lesions dried up and disappeared on the treated side; they remained intact on the untreated side. As for side effects, the Lanchow team wrote: "Camptothecine/DMSO solution, although locally irritating and somewhat odorous, is welcomed by our patients."

DERMATOLOGY

DMSO yielded generally good results in 16 of 23 cases of keloid and hypertrophic scars, 1 in 3 of induratio penis plastica, 6 of 9 of Dupuytren's contracture of the hand, 3 of 4 in scleroderma, 17 of 21 of eczema tyloticum, 6 of 9 infiltrative processes of the lower limbs, 4 of 7 sclerodermic changes in post-thrombotic syndrome, 3 of 5 granuloma anulare, 3 of 4 lichen ruber verrucosus, 2 of 4 verrucae vulgaris, 4 of 4 combustio, 10 of 11 herpes zoster and post-zoster neuralgia, 0 of 2 fibroma—75 of a total of 106 patients. [H. Weitgasser, Geibietskrankenkasse, Graz; *Zschr. Haut Geschl.-Krkh.*, Vol., 42, 18 (1967):749–54]

CREEPING ERUPTION

DMSO alone was applied to creeping eruptions on the skin of patients, and it proved of no benefit.

When DMSO in combination with 2 per cent thiabendazole was applied to creeping eruptions in 25 patients, all eruptions cleared up completely within three weeks. Thiabendazole, an anti-warm preparation, was dissolved in 90 per cent DMSO in these double-blind experiments. [Drs. Robert Katz and Robert W. Hood, Univ. of Miami, Fla., at AMA meeting in Chicago, June 1966]

SCLERODERMA

Scleroderma, a disease of unknown cause and with no cure, poses a formidable challenge to medical science. The crux of the problem seems to reside in a change in collagen, the gelatinous glue in the fibers which form muscles, tendons and other body structures.

Scleroderma can move swiftly or slowly through the victim; but, given enough time, it will turn to leather many organs and tissues, bringing death by roundabout routes—starvation when it paralyzes a part of the digestive tract, hypertension and heart attacks or strokes when it blocks the vascular system, and a long list of other troubles. It often is first noticed when ulcers appear on the fingertips, elbows and ankles. Gangrene eventually may set in on fingers or toes; skin patches may become white, taut and shiny; breathing problems occur when it thickens delicate lung tissues; and uremia may do the patient in when scleroderma injures the kidneys. Joints often become painful; muscles atrophy; the patient loses weight and becomes weak.

Scientists in two establishments have run extensive studies on patients—in the Cleveland Clinic in Ohio and in the

Department of Dermatology, Kazan Institute for the Advanced Training of Physicians in the Soviet Union.

Back in April, 1965, when DMSO still could be prescribed freely by doctors, Dr. Arthur L. Scherbel and associates in the Cleveland Clinic published a preliminary report on the results of DMSO treatment of 10 scleroderma patients.

Considering the relentless progress of the disease, Scherbel's results looked promising. Dr. Richard Brobyn, then with Merck, Sharpe & Dohme, which supplied DMSO, turned in a favorable report on the tests. Scherbel continued to treat the series and added to it other patients who joined up—totaling forty-two in all (27 women and 15 men aged 20–69 years). They had had scleroderma for from 1 to 25 years; and their conditions had been diagnosed variously as mild, moderate and severe.

The patients were given an elaborate battery of tests, these included extensive blood chemistries, x-rays, urinalysis, microscopic examination of biopsies of lesions. Doctors took EKG and EEG tests periodically, and they kept a record of such symptoms as flexed fingers and grip strength. For future reference, they made up charts of skin involvement (which occurred in all patients), toe and fingertip ulcers (in 19), digestive tract bleeding, obstruction and malfunction (in 25), chronic non-productive cough and other signs of lung impairment (in 21), heart symptoms (in 15), hypertension (in 5) and kidney trouble (in 4).

DMSO concentrations of from 30 to 100 per cent were swabbed on various areas of the skin or over the entire body until optimal strengths were established—on an average about 75 per cent, although the neck, face and armpits proved more sensitive than the back and extremities. After two or three weeks, only the hands, forearms and feet—and, occasionally, the face—were painted, three times a day for a while, then twice, and, finally, once a day. Some patients who did not respond to painting immersed their hands and

feet in a pan of DMSO, and they improved; immersion then became the treatment of choice for ulcers.

When the patients had been treated for from 3 to 23 months, Scherbel and his group sought to grade the progress made by each of the forty-three. A total of 26 had made good to excellent scores. Generally, those with the least disease on enrolling showed the greatest improvement. Skin and other readily accessible tissues responded well; finger and toe ulcers healed; normal or near-normal skin color returned and, as calcium deposits dissipated, underlying tissues softened; grip strength and movement of the fingers improved. Calcified joints, which had been injected with DMSO, progressively increased their range of motion. Excessive collagen wastes mounted in the urine until the deposits became largely depleted.

Three patients discontinued treatment after one year because all symptoms had disappeared, and they remained normal without treatment during at least six months of observation. Nine other patients felt well enough to discontinue treatment; but, within four weeks, pain and stiffness recurred and they resumed treatment.

Only two patients with far advanced disease scored good-to-excellent. One patient abandoned treatment because of pain on immersing her fingers; and 16 others advanced cases went on to make fair or poor scores. Six with severe disease died during treatment or within three months after it; so far as the scientists could determine, neither those nor any of the other 36 patients showed any ill effects due to the treatment.

Scherbel reported that most of the patients, relieved of pain, stiffness and weakness, were continuing treatment. He said the results of DMSO treatment have never equalled with any other kind of therapy. "It is the first time we have observed evidence, both clinical and histological, that the collagen is undergoing a definite change," he said.

The Russians—Drs. V. P. Sergeyev and R. Z. Zakyiyev—treated 58 scleroderma patients with DMSO.

Their ages ran from 10 to more than 50 years. The majority of those whose disease had become systemic were old, and they had had symptoms for more than 3 years; the majority of those with fairly localized disease were young, and they had been ill for less than three years. The condition in all cases was downhill.

As in Cleveland, the Kazan reserachers groped for optimal concentrations, starting with 90 per cent and working their way down. They found 50–70 per cent the most workable range; and having established the most desirable dose, they gently bathed the affected skin areas twice a day for anywhere from several months to two years.

The scientists reported that during the first two months the skin color in localized scleroderma started returning to normal, and the tissues under the skin softened. Where there had been atrophy, however, the skin blanched or turned gray and remained that way long after treatment had ended.

The improvement of these patients under treatment closely resembled that achieved in Cleveland. Only one with generalized scleroderma showed remarkable improvement, and that case resulted in a "clinical cure" after two years of treatment, the Russians reported.

The Soviet scientists remarked about the surprise and pleasure of the patients with the easing of their acute generalized disease. Patients commented on the suddenness with which the ugly old disabilities began to disappear and the rapidity of the healing process.

"Many patients in that group have said they were happy to experience washing with DMSO," the scientists said. "It reportedly improved their well-being immediately, and they simply could not imagine life without DMSO. The results we have obtained have proved the high effectiveness of DMSO."

SHINGLES

Shingles, a painful and sometimes extremely serious infection of nerve roots, is caused by herpes zoster, a relative of other herpes viruses which cause simple cold sores, chicken pox, a blinding eye disease, and infections of male and female genitalia which sometimes are associated with cancer of those organs, especially of the uterine cervix.

Shingles brings blisters of pinhead size to pea size, which follow the course of the infected nerve. Nerve (neuralgic) pain can be intense and long-lasting during the acute stage; and, especially in older people, a torturing postherpetic neuralgia may persist for months or years after the last blister has burst and dried up.

Oxford scientists wet strips of gauze with 40 per cent idoxyuridine and 100 per cent DMSO and kept them continuously over the sores of 22 zoster patients. The strips were rewet daily. In a median of two days—and nine days at the latest—the pain disappeared, and healing was accelerated.

The results were similar in uncontrolled and two double-blind clinical studies. [*British Medical Journal*, 4 (1970):776–80]

DNA VIRUS INFECTIONS

DMSO with IdU (5-iododeoxyuridine) cleared up skin lesions caused by DNA viruses and it prevented recurrence.

The treatment worked well, and in some cases spectacularly, on herpes simplex and zoster, chicken pox, and vaccinia. Among the 37 cases, every one showed healing in about one third the normal time.

Fresh cases healed rapidly and often completely. Older simplex cases took longer to heal and tended to recur; however, if the recurrence was treated promptly, healing was

very rapid and there was no tendency toward further recurrence.

The only "sequelae" reported was post-healing pain for three and seven weeks and six months in three of the eleven zoster patients. (Many shingles patients suffer pain for years after the clearing of their lesions.) [R.C. Turnbull et al., Otago Univ., Dunedin, *New Zeal. Med. Journal*, 70, 317:11/69]

FRIEND LEUKEMIA VIRUS

Cells containing a leukemia virus (Friend) were grown in glass dishes. When 2 per cent DMSO was added to the culture medium, the cells developed differently than they did when DMSO was not present. For one thing, they looked more like the normal cells which eventually give rise to good healthy red blood cells—maturation or differentiation, the normal "growing up" process is called. The DMSO-treated cells had their protein-producing structures (ribosomes) altered from those found in cells capable of inducing leukemia in mice; and evidence of hemoglobin synthesis tended to confirm opinions that DMSO might have a sort of "normalizing" effect on the cells.

The DMSO-treated cells contained numerous "budding" viruses. It is possible that the DMSO, by a chain of biochemical events still unknown, interrupted the cell's virus-manufacturing or virus-releasing processes. [Toru Sato, Charlotte Friend and Etienne de Harven, *Cancer Research* 31 (October, 1971):1402–17]

TUMORS

In the course of an outstanding career as a surgeon, scientist and director of one of the world's most productive cancer

research centers, George E. Moore, M.D., Ph.D., blazed many trails into the vast, bleak intellectual wilderness called cancer. For several years at the University of Minnesota, then as the organizer and head of Roswell Park Memorial Institute in Buffalo, N.Y., and presently at Denver General Hospital, he has explored the mysteries of cancer cells growing in laboratory dishes, in experimental animals and in patients, many of whom were beyond hope or help by othodox medical procedures.

In an exciting new phase of his wide-ranging studies to develop an effective tumor vaccine, Moore incorporated DMSO in his preparations. He felt the DMSO might transport the active antigen or antigens in cancer cells through the skin and enhance the immune reponse. A rub-on vaccine would eliminate the nuisance of injections. In the journal, *The Lancet* of June 5, 1976, he reported, "Penetration of the skin by the antigen is important. The addition of DMSO to DNCB, in a water-soluble base, and the use of an occlusive dressing have been helpful. Caution must be used since some local reactions may be severe in the axilla or in skin folds. Solid tumor metastases can be completely destroyed."

The number of patients at this writing is too few and the elapsed time too short to estimate the ultimate clinical usefulness of this technique. Moore feels that, in the light of his preliminary results, it should be a valuable method of determining the efficacy of topical, or rub-on, immune agents against benign and malignant tumors. DNCB (dinitrochlorobenzene) was one of several chemicals which he has found promising as an immunity booster. The common denominator among most of these drugs, when placed in contact with tumor cells, was an ability to increase the patient's immune response to various vaccines.

Once when he had to supervise the treatment of patients for a kind of venereal wart known as condyloma acuminatum, which probably is caused by one or more viruses, Moore was repelled by the "barbaric treatment" the condition called

for. The infections, which occur originally during anal intercourse, eventually seed such sensitive organs as the anus, rectum, penis, vagina, vulva and areas of the mouth and throat. When the warts were burned out by cautery or frozen in surgery, the pain often was exquisite. The growths also could be done away with by applying certain escharotics or anti-cancer drugs, almost all of which, Moore noted, boosted general immunity; one group reported that their vaccine made from venereal warts had made anal lesions disappear in 93 per cent of their patients. Would a rub-on do as well?

Moore's DMSO-containing vaccines worked well in condyloma patients—so well, in fact, that when the results reached the rumor market, the ensuing parade of gays overwhelmed the staff and the facilities of the hospital. It is impossible to calculate the percentage of success because, once rid of the warts, the patients speedily and silently returned to the anonymity from which they had emerged. Some had reported having been raped while in prison; others were paid counsellors of youngsters; only a few could discuss the homosexual origins of the warts without embarrassment.

The virus (es) of condyloma are of the papova family, some of which have caused a variety of cancers in several species of animals, including primates. Tests once showed that the ubiquitous polyoma virus, which has decimated mouse colonies, has infected humans too. Another papova virus, Simian virus-40, contaminated early batches of the polio vaccine and was injected into several hundered thousand Americans; while it causes cancer in monkeys, there is no evidence as yet that it has caused human malignancies. Nor is there good evidence that condyloma progesses into cancer. Moore's DMSO vaccines, and others' preparations too, are beginning to give hope that some cancers may prove as amenable to effective immuno-therapy, as warts seem to be. Vaccines have erased some cancers and their colonies.

Any progress, of course, depends upon the tolerance of the FDA. So far, Moore's work has been unimpeded. When he

implanted dimes in the bellies of rats and one third of them promptly came down with cancers, Moore said with a wry smile, "I'm going to ask the FDA to take coins off the market. Since money has proved to be carcinogenic, maybe we'd better test credit cards too."

Moore and an associate, Dr. William N. Palmer, published their work with coins later in a letter to the Journal of the American Medical Association under the headline: MONEY CAUSES CANCER: BAN IT. They called upon the government officers to "convene an emergency meeting for the purpose of removing all coins from circulation." They explained that their letter was a tongue-in-cheek reaction to the "string of inane pronouncements on cancer dangers" by the FDA.

Actually, Moore, over the years, had opened up an intriguing line of investigation in showing that different species reponded in various ways—with and without cancer—to substances embedded in their belly cavities. It all depended upon the size, shape (including thickness), form (solid or powder), and chemical composition of the substances.

A sober-sided Washington group, The Federation of American Scientists, which professes to act in the public interest, saw neither humor nor significance to Moore's letter, which others found pointed and hilarious. The Federation, in its monthly newsletter, quoted an unnamed scientist at the National Institutes of Health as calling the experiments "a misuse of cancer funds and of laboratory animals to make a humorous point."

Efforts to link DMSO activity with cancer gained theoretical significance with a series of discoveries during the 1970's indicating that one of its effects may be to somehow release cAMP, or cyclic adenosine monophosphate, in the cells. A veteran explorer of the world of atoms and molecules, Dr. Theodore Puck of the University of Colorado Medical Center, discovered about 1970 that cloned hamster ovary

cells with malignant structures were transformed into cells with normal structures when he exposed them *in vitro* to cAMP and the male hormone. Others discovered evidence that malignant cells were "normalized" when either cAMP or PGE (prostaglandin E) was added to the culture medium; presumably the PGE activated the enzyme (cyclase) which synthesized cAMP. Recently, a number of scientists have come to believe that DMSO's transformations of malignant cells and its arrest or reversal of incipient stroke and other effects are due to cAMP and PGE.

An ambitious project designed to test the effect of a variety of anticancer drugs in combination with DMSO was put to sleep by the FDA shortly after the first combination tested consistently had shrunk up the experimental rat tumor under study. The research by Dr. Joel Warren and his associates at Nova University in Fort Lauderdale, Fla., was halted by a jurisdictional dispute within the FDA just as preparations were being made for clinical trials at the University of Miami and the Florida Medical Center.

The transplanted cancer, if untreated, always killed the rats. It caused leukemia when it was transplanted into the belly cavity and solid lymphosarcoma if injected under the skin. The animals died rapidly—in ten to fourteen days from leukemia and three to four weeks from solid cancer. One FDA official was so enthused about the animal results that he felt human treatments were in order; he was outranked and outvoted by a rival within the bureau.

The most extensively tested drug was cyclophosphamide, or Cytoxan, a highly toxic chemical relative of nitrogen mustard; it depressed the white blood cell count and in high doses killed the rats and in low doses left them debilitated. DMSO added to the activity, including the toxicity, of the cyclophosphamide; and when both were administered in large doses, the rats died in short order. DMSO alone had no adverse effects, however.

When DMSO was given in a low dose—1 or 2 per cent in the drinking water, along with a low dose of the drug—the combination exerted a decided anticancer effect. If they were given early enough during tumor growth, they "cured" the transplants in a substantial percentage of animals.

Before FDA permission was withdrawn, the Nova group had tested in rats DMSO combinations with each of 16 drugs more or less widely used to treat human cancers; three of them—cytosine arabinoside, vincristine and 5-fluorouracil—were ineffective. Ten other drugs, however, showed particular promise in discouraging tumor growth and lengthening survival of the rats; they were 6-MP (mercaptopurine), methotrexate, chlorambucil, vinblastine, procarbazine, daunomycin, nitrogen mustard, dianhydrogalactitol, norbornyl, and adriamycin.

In a paper presented at a New York Academy of Sciences meeting, the group concluded: "Treatment of human cancer with combinations of oral DMSO and antitumor compounds is both feasible and attractive. Because of potential toxicity problems, it must be approached however, not only with caution but also under circumstances in which the maximum amount of information can be obtained on the mode of action of DMSO."

Of special interest in the Nova tests was the finding that DMSO traces, laced into the rats' drinking water, sped the disappearance of cyclophosphamide from the bloodstream and multiplied its concentration in cancer-susceptible organs, most importantly the brain. While several drugs are known to attack primary and metastatic tumors in such familiar sites as the liver, so far as is known, none of them can penetrate that formidable fortress of the mind, the blood-brain barrier. Should DMSO's unique transport properties enable it to carry other, nerve-healing, drugs into the brain, it may open new vistas of applications for psychotropic preparations.

INTERSTITIAL CYSTITIS

Interstitial cystitis, or IC, is a painful, often uncontrollable unflammation and irritation of the urinary bladder.

Under the guidance of Stanley Jacob, two teams were established to treat IC patients, one headed by Bruce H. Stewart, M.D., in the Department of Urology at the Cleveland Clinic, and the other by Sheridan W. Shirley of the Department of Urology, University of Alabama.

By the end of 1977, a total of 213 patients had received DMSO treatment for a variety of inflammatory conditions of the lower genitourinary tract—not only IC but also radiation cystitis, chronic prostatitis and chronic female trigonitis, or inflammation of the lower portion of the bladder. The investigators reported, "Significant symptomatic relief has been achieved in a majority of patients."

Actually, the data showed that 54 per cent of the women and 64 per cent of the male IC patients received good to excellent grades and remained on long-term therapy. Another 11 per cent of the women and 30 per cent of the men received relief of symptoms but later relapsed. Three of the 12 radiation cystitis patients received an excellent response, two good. For chronic prostatitis 75 per cent received good or excellent grades, and 74 per cent of the women with atypical chronic cystitis or trigonitis got good to excellent results.

A number of patients were referred with diagnoses which turned out to be false. Of the 14 men with chronic IC, many had been diagnosed as having prostatitis, and in 13 cases the prostate had been removed without relief of symptoms. Several more with a diagnosis of IC turned out to have bladder cancer, were sent to surgery and dropped from the study. All 35 patients with atypical chronic prostatitis had been operated upon without relief, but 26 of them improved under DMSO therapy. Three girls with inflammatory changes in the lower bladder and urethra responded well to DMSO.

URINARY CALCULI

One group of rats drank tap water. Another group drank water with 6 per cent DMSO—and when they lost weight because of the diuretic effect, the concentration was lowered to 3 per cent DMSO, on which they maintained normal weight. Both groups were fed a pelleted ration on which lambs had developed a high incidence of urinary calculi.

After two months, 40 of the 45 water-drinking rats had developed calculi of the kidney, bladder or ureter, while only 11 of the 46 DMSO group showed the calculi. Besides stones, the calculi also took the form of rubbery plugs, found mainly in the bladder. [Fu-ho Chen Cow, et al., Colorado State Univ., *Journal of Urology*, February 1967]

AMYLOIDOSIS

Amyloid is a waxy substance which exists in immeasurably small amounts in the normal human body. In amyloidosis, amyloid fibrils pile up in any of many organs and systems; its early signs are difficult to discern, but eventually it can turn the liver into a large, rubbery mass, depress or destroy the function of kidneys and spleen, pepper the skin with blisterlike tumors or rupture superficial veins, produce hemorrhages in the bowel and cause arrhythmias and heart failure. The lungs, thyroid and tongue may be involved.

A team of scientists at Sackler School of Medicine, Tel Aviv University in Israel, reported in a paper submitted in November, 1976, to the *European Journal of Clinical Investigation* that they had induced amyloidosis in mice and had cured it completely with DMSO injections. The scientists are Mordchai Ravid, Igal Kedar (Keizman), M. Greenwald and Ezra Sohar. The group induced amyloidosis by injecting mice daily for 18 days with vitamin-free casein and observed

them for the following 60 days, when the mice were killed and autopsied. The livers of mice treated with DMSO were completely free of amyloid deposits, although microparticles were found in the spleen. Control mice treated with salt solution or untreated presented livers and spleens loaded with amyloid. The DMSO-treated mice's urine began to show broken-up amyloid fibrils starting shortly after treatment and continuing until all the liver and almost all the spleen were free of amyloid. The researchers were able to remove the fragments from the urine and, in the laboratory, synthesize new amyloid from them. This seems to be the basis for a valuable, badly needed test for amyloidosis.

The Israeli team moved at once to human studies. Their first efforts were reported in *The Lancet*, April 2, 1977. Eleven patients who had amyloidosis, as determined by biopsy (tumor samples removed from the rectum and examined under the microscope), were given a test dose of DMSO, either intravenously or orally. Subunits of amyloid were found in the urine of all patients for the next 24 hours as the tumors began to break up. No traces of amyloid could be found in the urine of control patients with non-amyloid proteinuria diseases who were treated similarly with DMSO.

The research is continuing, to determine whether DMSO will cure amyloidosis in man as it does in mice.

TUBERCULOSIS

Thirty-two patients with destructive pulmonary tuberculosis complicated with TB of the bronchi and non-specific endobronchitis were treated with 10 per cent and 25 per cent DMSO solutions of streptomycin and penicillin, by inhalation and endobronchial infusion.

Most of the patients improved, and 14 ceased excreting TB mycobacteria. DMSO may be useful auxiliary treatment in

antibiotic-resistant disease. [V.I. Lyubinets and M.V. Kruk, Lvov, *Postunnula* 10, 11 (1969)]

RHINOSCLEROMA

Rhinoscleroma, caused by the bacillus Klebsiella, starts usually as a non-tender little lump in the nose and spreads as a stony mass to involve the breathing tubes and sinuses. Surgery, even effective, can be as mutilating as the disease.

DMSO dissolved the polysaccharide capsule coating the bacilli and permitted any of several antibiotics to destroy them; the combinations enhanced patients' normal resistance to the bacteria between 128 and 4,096-fold.

In one series, all 25 patients were cured. Diseased mucous tissues began falling away during the second week of treatment, and the solutions were dabbed or sprayed onto the wound. A combination of DMSO and prednisolone was used to prevent scar tissue from forming in the respiratory tract.

Long-continued monitoring of the patients showed no acute ill effects of treatment on the blood, urinary tract, respiratory system, eyes and ears. [R.A. Barilyak et al., Lvov Medical Institute, *Polish Literature*, 1968]

DIABETES

Scientists use a breakdown product of uric acid called alloxan to induce diabetes in laboratory animals. The alloxan destroys insulin-producing cells of the pancreas, thus depriving the body of its ability to get rid of toxic build-ups of blood sugar.

Dr. Richard E. Heikkila of the Mount Sinai School of Medicine in New York reported in the *European Journal of Pharmacology* in mid-1977 that DMSO injected into the

belly cavity of mice a half hour prior to their being injected into the tail with moderate to heavy doses of alloxan completely prevented the development of diabetes in the mice.

PARKINSON'S DISEASE

Controlled experiments in rats showed that L-dopa, the drug used with considerable success against Parkinson's disease, can be dissolved in DMSO and be transported into the brain where it is altered into dopamine, the active form of the drug. Another relative of L-dopa, called 5-HTP, also can be dissolved by DMSO and carried into the brain where it becomes active as dopamine. Dopamine can not cross the blood-brain barrier; the only way it can enter the brain and do its good work is in the form of L-dopa or HTP-and then let an enzyme in the brain (a decarboxylase) change it into active dopamine.

Efforts have succeeded to a degree in knocking out carboxylase on the blood side of the barrier. This is done with a chemical monkeywrench called DCI (decarboxylase inhibitor) which permits L-dopa and HTP to roam freely through the blood without fear of being changed to dopamine until it crosses the blood-brain barrier.

Using fluorescent strains, scientists have injected 1) L-dopa, 2) DMSO to transport it into the brain, 3) DCI (in this case called nialamide) designed to prevent blood carboxylase from changing L-dopa into dopamine; and they have been able to trace the L-dopa into brain capillaries and the nervous tissue where it became dopamine and turned off the brain functions which bring on the trembling and other symptoms of Parkinson.

This work so far has been done in rats. But because, in this particular phase of body chemistry, rats have behaved a good deal like humans, there may be hope for improved treatment

of Parkinsonism. [J.C. de la Torre, Univ. of Chicago, *Experientia* 26, 1117 (1970), Birkhauser Verlag, Basel]

NERVE REGENERATION

DMSO, with 1–3 per cent phenol combined with hyaluronidase, the enzyme known as the "spreading factor," was injected around the sciatic nerves of rats, who were observed clinically for six weeks, and then sacrificed and examined histologically.

Weakness and paralysis were proportional to the concentrations of phenol or DMSO injected. Myelin and axon destruction also depended on the concentrations of DMSO and phenol. But "the findings confirm the relatively few reports indicating that peripheral nerve will regenerate" and that, following nerve damage by 100 per cent DMSO, "nerve fiber repair occurs fairly rapidly." [Leslie W. Knott et al., Stanford Univ., *Neurology*, Vol. 19, October 1969]

STROKE

Dr. Jack C. de la Torre, Sc.D., at the University of Chicago School of Medicine, and Dr. P. K. Hill of the Mayo Clinic induced massive strokes in monkeys by exposing a middle cerebral artery and then closing it with a clip for 17 hours. During this time the brain became congested and inflamed with the dammed-up blood and fluids, and brain tissue began to die and decompose.

Four hours after inserting the clip, controlled experiments were begun on three groups of animals: 1) Six monkeys were given 50 per cent DMSO intravenously; 2) six were treated similarly with dexamethasone, a potent cortisone-type hormone which suppresses inflammation; and 3) six were given an inactive salt solution. Two other monkeys were sham

operated—their arteries were exposed but not clipped or closed; they came out of the operation in good shape.

All 18 animals were treated for 5 days, and 2 days after that were killed with overdoses of an anesthetic. The affected brain, nerve and blood vessel tissues were examined grossly and with light and electron microscopes.

In contrast to the sham-operated animals, varying degrees of damage were found in the tissue of the left side of the brain cortex which had its blood supply temporarily cut off. The right side of the brain was unchanged.

The examination left no doubt: DMSO, and DMSO alone, was able to prevent or clear up the ravages of simulated stroke in the animals. Control preparations fell far short of DMSO's dramatic performance.

In an article entitled "Ultrastructural Studies on Formation of Edema and its Treatment Following Experimental Brain Infarction in Monkeys" (published by Springer Verlag), de la Torre and Hill concluded that while dexamethasone protected the brain tissues from severe edema (swelling) to a degree, DMSO had proved useful in preventing great damage to brain tissues, cells and microscopic structures within cells. The saline-treated brains, as expected, were severely damaged and were rapidly degenerating.

The scientists reported that the dexamethasone-treated monkeys showed "severe neurologic deficits," fluid retention inside and outside brain cells, fragmentation of important internal cell structures, swelling of nerves and especially nerve ends, narrowing of a large (internal carotid) artery and consequent reduction of the blood supply to the brain (parietal) lobe which it serves. These animals also showed changes in the synapses, the "on-off switches" which connect lengths of nerves one to another. The result was poor recovery of sensory and movement functions.

In the DMSO-treated animals the damage was remarkably less: synapses were preserved, inter- and intracellular fluid

levels remained about normal, sensory nervous systems seemed minimally affected, the animals were alert; the only observable ill effects on movement were to the arm opposite the occluded side of the brain. The carotid artery didn't narrow; the blood vessels behind the block were less damaged and were repaired faster than in the other treated controls; DMSO protected the outer walls of nerve cells and the tiny structures inside from fragmentation; and vital cell functions—such as respiration, metabolism and energy generation—were maintained to considerable extent.

Dr. Manuel Dujovny and associates at the University of Pittsburgh showed in animal (dog) experiments that brain damage can be prevented or reduced following surgical removal of an artificial embolus blocking the middle cerebral artery supplying blood to the brain. If they removed the plastic block within five hours after inserting it into the artery, brain damage was negligible; after more than five hours the damage mounted rapidly. However, if they administered DMSO during surgery, as late as seven hours after blocking the brain artery there was little or no damage.

Dr. C. P. McGraw of the Bowman Gray School of Medicine at Wake Forest University, Winston-Salem, N.C., shut off the carotid artery of Mongolian gerbils, inducing stroke-type brain damage, and found that while DMSO administration caused larger lesions than saline solution did, DMSO wielded a protective effect on the blood supply and, in the right dosage, promoted healing.

SPINAL CORD TRAUMA

Dr. de la Torre and his group inflicted injuries of the spinal cord by dropping weights on the backs of test animals. The cord damage was similar to that incurred in automobile accidents—the kind that paralyzes people. Here too, animals given DMSO suffered a fraction of the mortality of control

animals treated with urea, Decadron, Mannitol, high pressure (hyperbaric) oxygenation, or several other agents. Moreover, DMSO reversed the paralytic process in many animals. Once again, it was important to treat the injured animals as early as possible; the recovery rate parallelled the shortness of time elapsed between injury and treatment.

DMSO also helped monkeys survive gunshot wounds in the brain, and it sped their recovery. No untreated animals survived wounds with high velocity missiles, as compared to 29 per cent survival of those treated with Mannitol and 100 per cent of those treated with DMSO. Treatment was given within 15 minutes of the wounding. With low velocity missiles 88 per cent survival occurred in animals treated with DMSO one hour after injury, as compared with 75 per cent in those given Mannitol.

Dr. de la Torre and others came to feel that DMSO would do well in brain and nerve injuries because of its numerous properties: diuretic, anti-inflammatory, assistance in white cell infiltration, prevention of scar formation, prevention of fluid accumulation and many other characteristics.

COMA

Dr. de la Torre's work in charting wavelengths in somatosensory areas of the brain cortex may prove useful in learning whether deeply comatose patients ever will recover. His first dozen predictions have proved 100 per cent correct.

HEART DISEASE

Drs. Marshal Shlafer and Armand M. Karow, Jr., of the Medical College of Georgia have noted a curious, seemingly contradictory, effect that DMSO has on heart muscle. The

researchers feel that their observations hold implications for the improved treatment of heart disease.

The scientists dealt in exceedingly dilute solutions of DMSO. DMSO concentrations of from 0.14 to 2.82 parts per thousand decreased the electrical response and, consequently, the beat of the heart. A rate of 2.82 also produced complete cessation of recordable heart beat; however, when the DMSO was washed off the tissue of the non-beating heart, the muscle resumed beating and regained its normal electrical properties. The tests were conducted at normal and a variety of subnormal body temperatures on hearts from cats, guinea pigs, rabbits and rats.

The investigators concluded that DMSO might be useful in treating heart conditions. "Simplistically," they reported at the New York Academy of Sciences conference, "these low concentrations can produce potentially beneficial or adverse cardiac effects in an *in vivo* [living] situation. Pending thorough studies of its mechanisms of action, DMSO could prove to be useful as a cardiac stimulant when used alone, as an inexpensive vehicle to potentiate the cardiac actions of other currently available therapeutic agents or agents yet to be discovered . . . or as an adjunct to cardiac surgery to enable the myocardium [heart muscle] to tolerate or recover better from stresses imposed upon it."

HEART PROTECTION

A total of 240 rats were given isoproterenol subcutaneously on two consecutive days. This caused portions of the heart muscle to die and decay, as sometimes occurs following a heart attack.

Surviving animals were divided into three groups: 1) one was given no treatment; 2) one was given 0.5 ml of 90 per cent DMSO subcutaneously daily; and 3) the other group was

given distilled water instead of DMSO. The animals were killed and autopsied at various times.

The water-treated and DMSO-treated animals showed hearts less damaged than those of the untreated, so far as necrosis was concerned. Moreover, the DMSO-treated showed not only less damage than the untreated, but the injury was of a different, milder, sort; and in them there was no evidence of heart muscle rupture or aneurysm.

The research was done in 1965 at Walter Reed Army Medical Center, but no journal would publish it at that time because of the FDA's attacks and ban on DMSO. [Arthur S. Leon (Newark Beth Israel Hospital) et al., American Association of Pathologists and Bacteriolgists meeting, May 1969]

LIMB BLOOD VESSELS

Twelve patients with various disorders of the limb arteries, veins and lymphatic vessels were treated with 1) a spray of 15 per cent DMSO to facilitate penetration of other drugs through their ill-nourished skins, and 2) a 60 per cent DMSO ointment and tincture to treat inflammation resulting from their circulatory disease.

"The good results show the usefulness of DMSO in the treatment of arterial, venous and lymphatic disorders of the limbs." [A. Kappert; Ang. Lab. Anna Seiler Hans Inselsp, Bern, *Schweiz. Med. Wschr.* 98 (46) (November 16, 1968)]

THYROID DEPRESSION

DMSO, at 5 and 15 per cent, depressed the activity (iodine uptake) of cultured mouse thyroids more effectively than did standard thyroid-depressing drugs (propylthiouracil and thiocyanate). The DMSO effect was reversed by simply washing the organ in water.

DMSO, at 63 per cent strength, exercised a small but significant thyroid suppressing effect when injected into mice. [Ronald F. Hagemann and Titus C. Evans, Radiation Research Laboratory, Univ. of Iowa College of Medicine, *Proc. Soc.* (1968): 1008–10]

CATARACT PREVENTION

Irradiated mice developed cataracts. If they were treated with DMSO—given topically to the eyes—8 minutes before 1,000 R to the head, lens opacification was not complete. While the lens was protected by DMSO, the cornea may have been made more radiosensitive. [R.F. Hagemann, Allegheny Gen. Hosp., Pittsburgh, *Radiology* 92, (1) (1969)]

RADIATION

DMSO protected cancer patients against the dermatitis—including erosion, blistering, itching and pain—caused by high energy rays. It also appeared to enhance sensitivity to the radiation and accelerate regrowth of normal tissues.

When one side of an irradiated area was given DMSO protection and the other side not, the protected side showed fewer ill effects. DMSO therapy was withdrawn in only one of 22 patients because of an eruption which was thought possibly due to DMSO. The fact that DMSO-treated areas showed skin reddening and exfoliation earlier (and more mildly) than untreated areas indicates that DMSO may have sensitized these tissues to x-rays; but DMSO also sped recovery. The skin darkening effect of x-rays was greater in the DMSO-treated patients.

The patients had cancers of the uterine cervix (12), breast and upper jaw (4) and breast and cervix (6). [Goro Irie et al., Hokkaido Univ. Sapporo, Japan]

MENTAL RETARDATION

Three scientific teams have tested DMSO in the treatment of mental retardation—in Chile, in Argentina and in the state of Oregon. Despite elaborate batteries of physical, biochemical and psychometric tests given the subjects before and during treatment, all the results must be considered preliminary. Definite improvement of several kinds were noted in the treated subjects; but some improvement was registered by controls who were having other medical treatment or none at all. The data make it clear, however, that DMSO-treated children scored higher than the controls when subjective observations and impressions could be ruled out completely.

The Chilean team was composed of Dr. Manuel J. Aspillaga and others at the Calvo Mackenna Children's Hospital in Santiago, Dr. Mila Sanchez of the Quilpué Hospital, and Dr. Lucila Capdeville of the Manuel Arriaran Hospital in Santiago. They treated 31 mongoloid youngsters with three amino acids essential to nerve funtion (GABA, GABOB, and acetylglutamine) dissolved in DMSO; the children received shots intramuscularly every day or every other day, with intervening periods when they received only capsules of the amino acids and no DMSO.

Since the odor of DMSO identifies the drug, the researchers did not administer placebos or attempt double-blind tests; the 27 mongoloid controls went untreated. Treated and controls were matched for various abilities and disabilities.

When the tests were over, DMSO-treated patients scored higher than controls for improvement in every category—motor ability, adaptation, speech and sociability. The difference in overall scores was considered mathematically "significant."

There was a difference in the score improvement made by treated young patients (under 3½ years old) and treated older patients (3½ to 14 years old). The younger ones showed, generally, more improvement than the older ones.

Moreover, their improvement was called significant in three areas (movement, adaptive and sociability), whereas the older children's scores were ruled statistically significant in only two areas: movement and "graphics" (improvement of appearance in still pictures and movies made of the subjects periodically during treatment).

The average intelligence quotient of the older group rose from 29 to 40 during treatment; the IQ of the controls remained about the same throughout. Scores in use and understanding of language rose among the treated patients, while the verbal scores remained unchanged in the controls.

All children in these tests showed a trait peculiar to mongolism, trisomy-21, which means that the cells contain three, rather than the normal two, twenty-first chromosomes. This aberration sometimes is a sign that leukemia may develop in the children.

The Santiago group concluded, "It seems to us that DMSO-amino acid therapy of children with trisomy-21 signifies an evident advance in the therapy of this syndrome."

In the Buenos Aires study, 13 non-mongoloid retarded children were treated for 180 days or longer with DAT, a combination of DMSO and amino acids. A control group of 13 children received conventional therapy. The causes of the illnesses included trauma at delivery, delayed breathing in the newborn, skull trauma, mother's measles when pregnant, encephalitis and a condition called kernicterus in which bile pigment is deposited in the brain and nerves.

Charts maintained during the treatment period graded each subject in point of visual/manual coordination, dynamic coordination, postural control, body's own control, perceptive organization, language age, ability to stand still, speed and head structure.

Highly significant progress was made by every DAT-treated patient, most often in every category graded. Controls, given standard physio, psycho- and chemo-therapy, made very little progress.

There were two tests in Oregon. The first was to gather comprehensive behavioral and psychometric data on 67 moderately and severely retarded children 4 to 17 years old, at the Pearl Buck Center, a private school for the retarded in Eugene, where the main campus of the University of Oregon is located. A control group was composed of 23 children whose parents would not permit treatment with DMSO but who matched the treated students in age, socioeconomic status, type and degree of mental retardation and other criteria.

The first study was conducted by Jean Gabourie, Janis W. Becker and Barbara Bateman of the Department of Special Education on the Portland campus.

The second was conducted by two physicians, Drs. Michael Dunn of the Eugene Hospital and Clinic and Stanley W. Jacob at the Medical School in Portland.

Both studies were adjourned while still in their preliminary stages, (the first after nine months, the second after three), because they ran short of funding and because one scientist, Gabourie, an essential researcher, had died suddenly of heart failure at the age of 43.

In this study, as well as the South American trials, no child was hurt by DMSO (which, in Oregon, was given orally in orange juice).

Jacob said he expects the investigation to go on when financial support becomes available. His impression is that the younger the child, the better the response to DMSO; and he intends lowering the minimum age when the tests are resumed.

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THE PERSECUTED DRUG: THE STORY OF DMSO

"Research Industries is
Cleared to Market 'Miraculous' Drug"
"Joint Effort Bends FDA Arthritis Drug Now OK"
"FDA to Approve Disputed DMSO for Human Use"
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DMSO, dimethyl sulfoxide, a by-product of the paper manufacturing process, was hailed in the early sixties as a "miracle drug," and then banned by the FDA. This is the story of its discovery, of the man who has dedicated his life to freeing DMSO for common use, and of the amazing properties of this drug of the future.

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